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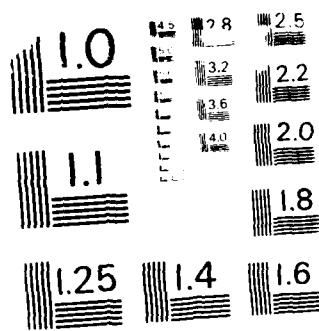
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Development of Microcomputer Methods for  
Analysis and Simulation of Clinical  
Pharmacokinetic Data Relevant to New  
Drug Development

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Annual Report

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Division of Clinical Pharmacology  
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The work performed during the past twelve months of the contract includes the following:

1. Continuing development of a non-linear pharmacokinetic data fitting program to analyze drug data where non-linear processes are responsible for some of the drug disposition pathways.
2. Development of a pharmacokinetic and pharmacodynamic data simulation program to simulate both time courses of drug concentrations and pharmacologic effect.
3. Continuing development of a statistical program package applicable to problems in clinical pharmacology, involving both parametric and non-parametric tests.
4. Development of a pharmacokinetic simulation program based on differential equations, intended to simulate time courses of concentrations of drugs exhibiting non-linear kinetics.
5. Initial development of a quantal (probit) dose-response analysis program.
6. Special analysis of data from WRAIR, one on a comparative bioavailability study of mefloquine, the other on methemoglobinemia induced by primaquine and related compounds.

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## SUMMARY

The research proposed under this contract is a feasibility study in the development of applications of new microcomputer graphics technology to the analysis and interpretation of clinical pharmacological data. This involves continuing development of comprehensive programs for analysis, interpretation, and simulation of pharmacokinetic data, dose-response kinetic data, and other data relevant to new drug development, for use with the Tektronix 4052 Microcomputer Graphics System. The combination of such modern analytical and illustrative methods in clinical pharmacology, based on new high-speed microcomputers and associated graphics, are thought to greatly reduce both cost and time involved in the overall process of clinical evaluation of new drugs in the U.S. Army Drug Development Program.

The work performed during the past twelve months of the contract includes the following:

1. Further development of a non-linear pharmacokinetic data fitting package to analyze drug data in systems where some non-linear processes are responsible for transport or metabolism of the drug (e.g. Michaelis-Menten kinetics). This is a continuation of work begun last year. Some of the causes for the disappointing slowness of the original programs have been identified, as well as some limits on the degree of improvement which is achievable.
2. Creation of a pharmacokinetic and pharmacodynamic data simulation program which enables the user to simulate the time course of drug concentration and effect. This program extends the capabilities of our previously developed pharmacokinetic simulator to allow the examination of effect vs time relationships for various drug dosing regimens. The user can now have graphs of the predicted concentration and/or effect data resulting from any type of dosing regimen, with the same ease of use and flexibility available from the original pharmacokinetic simulation program.
3. Additional work on statistical programs for clinical pharmacology. One of our main efforts in the statistical package was the implementation of several multiple-comparison tests. These tests are particularly useful in simultaneous comparative studies of several drugs, allowing comparison of all possible sets of competing treatments in order to quickly isolate the most promising for further study. This enables more efficient use of time and money in testing new experimental courses of treatment, reducing the development cost of new drugs.

4. Development of a pharmacokinetic simulation program based on differential equations. This program is intended to be used as a companion to the non-linear pharmacokinetic data analysis package, allowing the prediction of time courses of drug concentrations due to various dosing regimens in systems characterized by rate-limited processes of drug transport and/or metabolism. It provides functions similar to those available in our linear pharmacokinetic simulator, which was previously developed.

5. Work on a probit (quantal) dose-response analysis program. This type of pharmacodynamic analysis is commonly used in studies involving responses of a discrete, categorical nature, rather than the continuous effect data which is dealt with by our previous dose-response analysis program. The two techniques can overlap somewhat if the discrete responses are converted to percentages of some total available response. If this is done, the two programs produce very similar results for the ED-50, or median effective dose, but the bounds placed on this estimate are sometimes quite different. This discrepancy between the two methods is a matter we intend to examine further during the coming year.

6. Special analysis of data from the Walter Reed Army Institute of Research. Two requests were received for assistance with data analysis in connection with drug development experiments being performed at WRAIR. One was from LTC Charles Pamplin, asking that we analyze the results from a comparative bioavailability study of two formulations of mefloquine which was performed on 12 normal subjects using a cross-over experimental design. This experiment was complicated by the fact that one of the subjects was mistakenly given the two treatments in the wrong order, resulting in an unbalanced study. We have managed to successfully overcome this difficulty in the analysis, and are currently preparing a final report on the results.

The other special request came from CPT John Anders, who has performed experiments on the degree of methemoglobinemia in dogs given primaquine and several new antimalarial compounds under development. One of his questions involved the pooling of results from the primaquine-treated groups in two different experiments, in order to obtain a larger sample and thus greater statistical power. The analysis of his data also involved the use of some of the multiple comparison methods we have developed this year, which are discussed in this report.

## BACKGROUND

The process of drug development has been both complicated and facilitated by the trend toward early application of the methods of clinical pharmacokinetics. Current practice and existing and proposed new Food and Drug Administration Regulations demand sophisticated evaluation of drug bioavailability and descriptive pharmacokinetics in Phase I clinical studies. This requires development of assay methods for new drugs and their metabolites and methods for evaluation of concentration vs time data to obtain relevant parameters to characterize drug behavior. Of similar importance is knowledge of characteristics of relationships between dose or concentrations and pharmacological response. The information thus obtained from pharmacokinetic and pharmacodynamic studies relates directly to the optimal design of dosing schedules of new drugs in man, including individualization of therapy due to disease processes or other factors which may affect drug behavior. In this regard the eventual course of development through Phase II and Phase III clinical studies is rendered less empirical and ultimately more efficient in both time and cost, by minimizing the use of scarce resources.

Modern computer technology has greatly enhanced the capability of these methods and made possible their applications to clinical pharmacokinetics. A number of available computer programs have been frequently employed for this purpose. Those which have been developed for use specifically in clinical pharmacokinetics are based on compartmental methods of analysis and yield estimates of parameters associated with preselected compartmental models. While useful and informative, they lack the ease of use and cognitive appeal of direct graphic simulations and graphics-assisted data analysis. It is in the interest of developing general purpose programs with the advantages of computer graphics that the present contract was initially pursued.

Previous experience with the Tektronix 4051 and 4052 Microcomputer Graphics Systems indicated that this was an especially suitable microcomputer system for our purposes. While similar systems are now available from a variety of sources, it is in the interest of conformity with existing systems in the U.S. Army Drug Development Program at the Walter Reed Army Institute of Research that the Tektronix System has been employed. The present Tektronix 4052 System in our laboratory and for which the programs to be described were developed is identical to that now in use at Walter Reed. A data communications interface has been installed to facilitate direct transmission of programs and data between these two facilities.

## PROGRESS

### A. Non-linear Pharmacokinetic Data Analysis Package Using Differential Equations.

This program package, on which work was begun last year, is intended to be used for fitting data to a model involving some non-linear kinetic processes. Such systems cannot be analyzed by model-independent methods such as our linear pharmacokinetics program package, developed earlier under this contract. Because it is important to be able to characterize these data in cases where a new drug shows evidence of some rate-limited or time-dependent kinetic behavior, this package has been designed to allow the fitting of a model described by a system of differential equations, which need not be restricted to the linear, first-order models used for simpler pharmacokinetic analysis. In developing this package, we have tried to retain many of the "user-friendly" aspects of our other pharmacokinetics package, including extensive graphic interaction for verification of data values and initial estimates of the model parameters. The detailed statistical analysis of the results of the fitting procedure has also been retained, although not as much information can be derived by the program with regard to clearance terms, volumes of distribution, or half-times, since the program has no knowledge of the meaning of the model parameters other than time and concentration in the sampling compartment.

The principal reason for our dissatisfaction with the program last year was the fact that complete analysis of one set of data took much longer than a similar problem would using the linear pharmacokinetic analysis package. A number of possible solutions for this difficulty were tried, specifically including testing several different algorithms for the numerical integration of the system of differential equations which describes the model. These attempts were only somewhat successful, for reasons which became apparent after trying many of the different methods. One of the main difficulties in numerically solving a differential equation system is the choice of an appropriate step-size to use in moving from one observed data point to the next. Sophisticated methods exist for adjusting the step-size so as to maintain the desired level of accuracy without taking more steps, and time, than necessary. However, due to the unequal spacing frequently found between successive observations in pharmacological studies, automatic step-size adjustment becomes impractical, because the solution must be restarted for each new interval, and the resulting increases in overhead and bookkeeping in the program waste most of the time saved by using the more elaborate algorithm. A further cause for the slowness of the program is the fact that the numerical integration of the model with respect to time must be followed by a stage of numerical differentiation with respect to all the other parameters. This is in marked contrast to the linear pharmacokinetics program, which uses analytic derivatives which have been written

into the code. We feel that this may be the most time-consuming step in the solution process, and that further attempts to reduce the running time would not be productive enough to justify the effort. Therefore, to simplify the program, the complex predictor-corrector method which was being used has been replaced by a fourth-order Runge-Kutta integration technique, along with a simple means of determining step size. These changes reduce the size of the program significantly, and should also make it easier to maintain and modify in the future.

#### B. Pharmacokinetic and Pharmacodynamic Simulation Program.

This program is an extension of our earlier pharmacokinetic simulator to add the capability of predicting the time course of effect of a drug, based on the predicted concentration and on a concentration-effect relation like the one used in our program for pharmacodynamic analysis. The resulting program allows the user to request that the predicted effect be plotted against time alone, or with the predicted concentrations as well. If concentrations are to be graphed, they may be shown on linear or logarithmic scales, as in the original program. The effect axis is always linear and will be automatically scaled by the program, but the user may override the choice of endpoints and tic intervals if desired, another feature which has been retained from the earlier program. A new capability with this version, which is most useful when drawing graphs using the Tektronix plotter, is the pause feature, which stops the pen after drawing the axes and labels, and again after the concentration curve and before the effect curve, allowing the changing of pen colors for different sections of the plot. In addition to these changes, some other improvements have been added to reduce the drawing time of the program, resulting in a more uniform line width on the paper, which is less likely to smear. This program should prove most useful in designing drug dosage regimens on the basis of some desired range of effectiveness, such as to maintain a minimum effective level, or to avoid a level of effect which is associated with negative drug reactions.

#### C. Statistical Program Package for Clinical Pharmacology.

Most of the development of the statistical program package this year has been concentrated on the problem of performing multiple comparisons among several groups of data without inflating the apparent significance of the results. This problem can occur frequently in pharmacology research in situations where a pilot experiment is performed on a number of new drugs or methods of treatment in order to determine which is the most promising for further investigation. A similar situation arises when an established standard compound or formulation is to be compared against several new ones, to see if there are differences in quality. The difficulty with this type of comparison is that the various subsets of the data that are to be contrasted are not generally independent, and this

can lead to stated probability levels which are much more significant than the actual test result ("false positives"). The techniques used for avoiding this problem all involve making the individual comparisons at more stringent probability levels, so that a statement can be made about all the tests simultaneously at an overall significance level of 0.05 or 0.01 or whatever level is desired. Procedures for doing this have now been added to our non-parametric analysis of variance program, the Kruskal-Wallis test for one-way classifications, and the Friedman test for data in a two-way layout. Additionally, we have written a program for the parametric one-way analysis of variance with multiple comparisons, using the Bonferroni method for adjusting the significance levels. Two other tests are being investigated for the parametric analysis of variance program: Dunnett's test for comparing all other treatments vs a control or standard; and Duncan's for all possible comparisons. Because these methods currently require the use of tabular values in order to apply the tests, we are hoping to find a way to have the necessary critical values computed within the program, making it more useful. One other development for the statistical program package has been the beginning of a method for analyzing data from unbalanced cross-over design studies. This problem was brought to our attention in connection with the analysis of mefloquine bioavailability data requested by LTC Charles Pamplin. Because a cross-over design may easily be upset by accident, or by uncooperative subjects, the ability to analyze data resulting from an unbalanced experiment is most important in order to learn as much as possible from the completed sections of the study. We intend to do further development work on this program in the coming year.

#### D. Non-linear Pharmacokinetic Simulation Program Using Differential Equations.

This program complements the capabilities of the non-linear pharmacokinetic data fitting package by allowing the prediction of concentration vs time curves for the same kinds of kinetic models defined in terms of sets of differential equations. In this, it may be even more valuable than our linear kinetic simulator in helping people to visualize the effects of changes in dosage regimens, since the non-linear models are more difficult for most people to grasp intuitively. As much as possible, we have tried to make this program as easy to use as the corresponding linear one, with the same options for such features as titles, axis ranges, and log/linear scaling. In addition, this program also has the pre-computation of the entire time-course before drawing the graph in order to reduce the drawing time and produce a more uniform looking graph. The only significant feature not yet available in the non-linear simulation program is the ability to make effect predictions based on the sample compartment concentration. This section has been left out of the current version of the program not because of any problem with implementation, but instead because we do not know of any good source of data concerning concentration-effect relations in non-linear kinetic models. Without such a source, this portion of the program cannot be properly tested.

#### E. Quantal Dose-Response Analysis Program using Probits.

The purpose of this program is to allow the analysis of dose-response data in situations where the measured response is discrete or categorical, rather than the continuously variable responses dealt with by our earlier pharmacodynamic analysis program. Categorical data can arise in many different circumstances, including experiments where the response can only be roughly measured and those in which the response is an event which has an all-or-nothing character, such as death in an LD-50 study. The method used for analyzing such data involves converting the percentage responding at each dose level into probability units, or probits, and then performing a linear regression of probit response vs log dosage. This has the effect of fitting a cumulative normal probability curve to the dose-response data. Because of the nature of this curve, the initial fitting is not usually sufficiently accurate to fully describe the data. To correct this, weights are assigned to each data point based on its position on the initial regression line, and a new weighted regression is computed. This process is then repeated, with new weights drawn from the new regression line. This cycle is repeated until the values at two successive stages of the iteration are judged sufficiently close. The program runs fairly quickly, with convergence to a final answer typically occurring after four to eight cycles of this re-weighted regression. The resulting line corresponds to a normal probability curve, with the mean representing the ED-50 and the standard deviation giving a measure of the sensitivity of the effect to changes in the dose. During comparison of this program to the logistic pharmacodynamic data analysis program, we obtained very consistently comparable estimates of the ED-50.

#### F. Special Data Analysis Requests from Walter Reed.

Two major analysis projects were performed this year at the request of researchers from the Walter Reed Army Institute of Research. One, requested by LTC Charles Pamplin, involved the treatment of data from a cross-over design comparative bioavailability study of two tablet formulations of mefloquine. This was somewhat similar to an earlier analysis of data which we performed in the previous contract year. The second analysis project, for CPT John Anders, was an examination of measured methemoglobinemia in dogs, caused by dosing with primaquine or with new experimental antimalarial compounds. Details on both of these analyses follow.

LTC Pamplin asked us to analyze the data from a study performed by Bio-Med, Inc. for WRAIR on the comparative bioavailability of two tablet formulations of mefloquine, lot E555 prepared by Lafayette Pharmacal and a second prepared by Hoffman-LaRoche. The study was intended to be a balanced cross-over experiment, with 12 normal subjects receiving both preparations, with half the subjects to be given the tablets in one order

and the other half in the reverse order. Since it was assumed that the volume of distribution and rate of elimination of mefloquine in a given individual would be independent of the formulation given, our analysis focused on possible differences in the rate of absorption and in the fraction of the total dose which was actually available. This analysis was complicated by two factors. First, due to the withdrawal of one of the original test subjects during the study, a replacement was added, but he was inadvertently given the formulations in the reverse order of the individual who left the study. This resulted in an unbalanced cross-over design, which complicated the statistical analysis. Second, due to the long half-life of mefloquine, a significant amount of residual drug from the first dose was still present in the subjects when the second formulation was administered. This fact complicated the pharmacokinetic analysis. Nevertheless, we were able to perform a detailed analysis of the data, as summarized below.

The data regarding dosing order, times of administration, body weight, measured concentrations during the study, etc. were transmitted through telephone lines from WRAIR to Duke, using the data communications interface of our Tektronix 4052. After receiving this set of data, we performed some extensive reformatting to enable the subsequent pharmacokinetic analysis steps to access all the data. Two principal steps were taken in the kinetic analysis of the concentration vs time data. First, the area under the curve was calculated using a combination of the trapezoidal rule and extrapolation beyond the last data point based on the terminal exponential curve. For each subject, this calculation was performed in such a way as to force the exponential slopes after the first and second doses to be identical. In addition, the area under the second dosing interval curve was corrected for the carry-over of the exponential tail from the first dosing interval. Second, a non-linear regression analysis was performed, fitting the concentration data to a model which allowed different absorption rates and fractional availabilities for the first and second doses, but kept the volume of distribution and elimination rate terms identical during both dosing intervals. The resulting collection of pharmacokinetic parameters was then statistically analyzed, using an analysis of variance model for an unbalanced cross-over design. The results of this analysis showed a consistent and statistically highly significant pattern of differences between the two formulations. The data conclusively showed that the Hoffman-LaRoche preparation was more rapidly and more completely absorbed. In addition, this project showed that useful data can be obtained from bioavailability studies in which there is some interference between successive stages, and from imperfect experimental designs. Preliminary results from this study have already been sent to WRAIR, and a final report is currently being prepared for submission.

CPT Anders requested our assistance in analyzing data from two experiments which dealt with methemoglobinemia in dogs caused by primaquine or by one of several new experimental antimalarials. In the first experiment, primaquine was compared with WR238605, WR225448, and WR242511. In the second, primaquine was compared with WR6026. In both studies, molar equivalent doses of the drugs were given. The objective of this analysis was to compare all the drugs to determine if any statistically significant differences in methemoglobinemic potential existed. Prior to making such a comparison, however, we had to verify that the primaquine data in the first experiment was comparable to that in the second, so that pooling of these two sets of data would be legitimate.

Data from a total of 19 dogs were presented for analysis. The desired comparison was to be on the basis of percent methemoglobinemia (Mhb) caused by administration of one of the antimalarial compounds in four daily doses. Because of the significantly non-zero baseline (pre-dose) values of methemoglobin in the dogs, corrections had to be made in order to compare only the effect of the drug. This was achieved by fitting each dog's Mb vs time data to a model based on a one-compartment kinetic system with first-order input, modified to have a non-zero baseline as one of the model parameters. The results of this analysis were then treated with both parametric and non-parametric analysis of variance procedures with multiple comparison testing, as described earlier in this report. The parameters tested were baseline Mb, rate of increase during dosing, rate of decrease after dosing, theoretical initial Mb level, and total area under the curve above baseline. Preliminary comparison of the primaquine data from the first and second experiments showed no significant differences, so these two groups were pooled for all subsequent analyses. The results showed no pattern of differences between groups for baseline, nor for rate of Mb increase or decrease. Statistically significant differences were found in the theoretical initial Mb level and in the area under the curve, with WR242511 being significantly higher than any of the other groups. No other significant differences were detected by this procedure. In particular, the new compound which resulted in the lowest Mb levels, WR6026, was not significantly higher than primaquine, which was lowest, under direct comparison. A detailed report on the results of this analysis has been submitted, and a copy is attached as an appendix to this report.

Technical Report

Statistical Comparison of Methemoglobin-Producing  
Potential of Five 8-Aminoquinoline Antimalarial Drugs

September 21, 1983

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## INTRODUCTION

CPT John Anders of the Walter Reed Army Institute of Research presented data from two experiments, involving a total of 19 subjects (male beagles), concerning the methemoglobinogenic potential of five different 8-aminoquinoline antimalarial drugs. The purpose of these experiments was to compare primaquine, WR2975, with four new compounds, WR238605, WR225448, WR242511, and WR6026, with respect to the degree and duration of drug-induced methemoglobinemia. The analysis of the data was complicated by the fact that there were significant levels of baseline methemoglobin which had to be taken into account in order to compare the different drugs. An additional concern dealt with the fact that control groups in each of the two experiments were given primaquine, but it was not known whether these two groups could be pooled together. These problems were solved, using nonlinear regression analysis to describe the production and elimination of methemoglobin in each dog, and using parametric and nonparametric statistical methods for comparing multiple groups. The results showed some very important differences among the drugs, and indicated that two of them, WR238605 and WR6026, would be the most promising for further investigation.

## METHODS

The initial problem faced in analyzing this data was the choice of an appropriate model to describe the time course of methemoglobin formation and elimination in the individual dogs. Because no information was available on the drug concentrations, it was not possible to perform a simultaneous pharmacokinetic and pharmacodynamic analysis to describe the time course of drug concentration and the concentration-effect relationship between drug concentration and methemoglobin level. This forced the choice of a simpler pharmacokinetic model to fit to the data. In addition, the model had to be modified to take into account the baseline levels of methemoglobin, which were quite high in some cases, and which varied widely among different animals. The model finally chosen was a single-compartment multiple-dose kinetic system, with first-order input and output, with an additional constant term to correct for baseline. The parameters of this model were baseline,  $C_0$ ,  $k_a$ , and  $k_{el}$ . The baseline term reflects the initial pre-dose level of methemoglobin, based on one week of baseline data, as well as the limiting terminal concentrations at the end of the experiment.  $C_0$  is usually interpreted as the theoretical concentration at time 0, if instantaneous drug absorption were to take place. In this case,  $C_0$  represents the initial percentage methemoglobinemia which would result if both drug absorption and drug-caused methemoglobin production took place instantly.  $k_a$  is normally a measure of drug absorption rate; in this model it probably reflects both the absorption rate of the drug and the rate of formation of methemoglobin.  $k_{el}$  is usually taken to represent the drug elimination rate; in this case it may be a measure of elimination of drug or methemoglobin, or a combination of both processes. Using this model, nonlinear regression analysis was performed on each individual animal's methemoglobin measurements. The resulting fitted curves were examined to see if the model adequately described the data. The results were surprisingly good, showing no pattern of deviations that would suggest a more complex model was needed. The parameters describing these individual curves were then tabulated and summarized to prepare for the statistical comparisons to be performed. An additional descriptive parameter was computed, the area under the curve (AUC). This is the integral of the level of methemoglobin due to drug across time, after correcting for the baseline values. AUC provides a measure of the total methemoglobinogenic impact of a particular drug, since increases in level or duration of effect will cause increases in AUC.

After computing the best-fitted curves for each set of data and collecting the resulting parameters, statistical testing was performed, using both parametric and nonparametric techniques. The primaquine control groups from the first and second experiments were compared and found to be well-matched, so these groups were pooled together for all subsequent comparisons against the other drugs. The data were classified into groups based on which drug had been given, and these groups were then

tested for any significant difference using the classical one-way analysis of variance and its nonparametric equivalent, the Kruskal-Wallis test. These procedures for detection of overall differences were augmented by multiple comparison procedures to allow pair-wise testing of groups in order to isolate the areas where important differences were found. These methods are designed to control the likelihood of a so-called Type I error, that is, concluding that a significant difference exists when the actual cause is random variation. In this study, the possibility of a Type II error, failure to detect a real difference, was also a great concern. Therefore, additional tests were performed in order to assure that those groups which were declared "not significantly different" were truly comparable.

## RESULTS

The individual parameters from the curve-fitting procedure are listed in Table 1, along with groups means and standard deviations and overall means and standard deviations. The results of the statistical tests by parametric and nonparametric methods were almost identical, with both approaches finding significant effects in  $C_0$  and AUC, but no systematic differences in any of the other parameters. Baseline methemoglobin levels seemed to be a random characteristic of each dog, and  $k_a$  and  $k_{el}$  showed no patterns of being faster or slower for any particular drug. The multiple comparison procedures showed that WR242511 caused significantly higher methemoglobin levels, as measured by  $C_0$  and AUC, than primaquine, WR238605, and WR6026. There was also a smaller significant difference between WR225448 and primaquine. When individual tests were performed to maximize the power of detecting small differences, no statistically significant differences were found between primaquine and WR238605, nor between primaquine and WR6026. These two compounds would appear to be the most promising for further study, since when given in equimolar amounts as primaquine, they cause no significantly higher levels of methemoglobinemia.

Table 1: Summary of parameters of fitted curves describing the time courses of methemoglobin levels in individual animals.

	Baseline	$C_0$	$k_a$	$k_{el}$	AUC
<b>WR2975</b>					
2A30	0.4321	1.432	0.07981	0.008743	163.8
2A20	1.0458	1.320	0.04248	0.009592	137.6
2A21	4.5192	2.741	0.05370	0.006564	417.6
2D93	6.3253	3.030	0.02039	0.020385	148.6
2D95	0.4711	0.958	0.07285	0.008483	112.9
<u>2D96</u>	<u>2.6197</u>	<u>1.903</u>	<u>0.13725</u>	<u>0.002596</u>	<u>733.1</u>
Mean	2.5689	1.897	0.06775	0.009394	285.6
S.D.	2.4167	0.828	0.04020	0.005938	246.2
<b>WR238605</b>					
2A23	0.3714	10.824	0.01487	0.006170	1754.3
2A26	0.3487	5.565	0.00690	0.006896	806.9
<u>2A31</u>	<u>1.9596</u>	<u>2.993</u>	<u>0.02122</u>	<u>0.001357</u>	<u>2205.6</u>
Mean	0.8932	6.460	0.01433	0.004808	1588.9
S.D.	0.9236	3.992	0.00718	0.003010	713.9
<b>WR225448</b>					
2A25	2.2463	7.470	0.05045	0.001673	4465.5
2A22	1.4132	13.387	0.01012	0.005126	2611.8
<u>2A27</u>	<u>0.2983</u>	<u>5.513</u>	<u>0.01764</u>	<u>0.003728</u>	<u>1478.8</u>
Mean	1.3193	8.790	0.02607	0.003509	2852.0
S.D.	0.9774	4.100	0.02145	0.001737	1507.7
<b>WR242511</b>					
2A28	1.2719	15.193	0.06037	0.004330	3508.5
2A24	0.9122	17.584	0.02744	0.004116	4272.3
<u>2A29</u>	<u>0.9842</u>	<u>18.623</u>	<u>0.01665</u>	<u>0.006048</u>	<u>3079.0</u>
Mean	1.0561	17.133	0.03482	0.004831	3619.9
S.D.	0.1903	1.759	0.02278	0.001059	604.4
<b>WR6026</b>					
2D94	4.2800	5.042	0.07176	0.004314	1168.9
2D97	4.1263	6.792	0.07178	0.004271	1590.2
2D98	0.3562	7.188	0.03571	0.007487	960.0
<u>2D99</u>	<u>4.2543</u>	<u>2.574</u>	<u>0.07952</u>	<u>0.004431</u>	<u>580.9</u>
Mean	3.2542	5.399	0.06469	0.005126	1075.0
S.D.	1.9332	2.102	0.01966	0.001576	420.9
Mean	2.0124	6.849	0.04689	0.006122	1589.3
S.D.	1.8269	5.642	0.03341	0.004143	1405.2

TECHNICAL REPORT

BIO-MED EXPERIMENT #10

COMPARATIVE BIOAVAILABILITY OF TWO TABLET FORMULATIONS OF MEFLOQUINE HYDROCHLORIDE

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## Introduction

A series of oral formulations of mefloquine were produced during the development of this new antimalarial drug. The first to be used in Phase II therapeutic trials was a 250 mg (mefloquine-HCl) capsule manufactured by Lafeyette Pharmacal. Results of these initial clinical trials suggested limited bioavailability of the capsule formulation. A subsequent 250 mg (mefloquine-HCl) tablet formulation, E443, also manufactured by Lafeyette Pharmacal was more successful therapeutically.<sup>1</sup>

A later 250 mg (mefloquine-HCl) tablet formulation, B512, was prepared by InterRx with in vitro dispersion superior to that of E443. Extended Phase I safety, tolerance and pharmacokinetic studies with the new formulation, B512, suggested that at doses in excess of 1000 mg, it was not as well tolerated as E443 had been in earlier studies. A comparative oral bioavailability study with B512 and E443 demonstrated that the former was more rapidly and possibly more completely absorbed than the latter.<sup>2</sup>

A new lot, E555, of 250 mg (mefloquine-HCl) tablets was prepared by Lafeyette Pharmacal according to the same formulation as E443. A tablet containing 250 mg mefloquine base (approximately 275 mg mefloquine-HCl) was also prepared by Hoffmann-LaRoche, Basel, Switzerland (HLR) for use in clinical trials supported by Hoffmann-LaRoche and under the auspices of the Steering Committee on the Chemotherapy of Malaria (CHEMAL) of the WHO World Bank WHO Special Program for Research and Training in Tropical Diseases (TDR). The present study was conducted to compare the oral bioavailability in normal healthy volunteers of the E555 and HLR tablet formulations.

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### Study Design and Methodology

This was to have been a standard randomized balanced cross-over study in which the safety, tolerance and oral bioavailability of a single 1000 mg (mefloquine·HCl) dose of the E555 formulation (4 tablets) would be compared with a single 1100 mg (mefloquine·HCl) dose of the HLR formulation (4 tablets). Both formulations were to be administered in random sequence to each of 12 volunteers in three groups of 4, with an interval of 28 days between the two doses. One of the participants (#263) failed to return for the second dose and was replaced by a 13th individual (#273). However, the replacement, #273, was given the two formulations in the opposite sequence assigned to the original participant, #263. Therefore, the resulting study was an unbalanced cross-over. While the data are still amenable to analysis there is a loss of power to detect significant differences because of this circumstance.

The sequence of administration to each of the volunteers is shown in Table 1, where A designates the HLR and B the E555 formulations. It should be noted that in this study the dose of mefloquine administered to each individual was not exactly the same for the two formulations. This was due to the fact that HLR was manufactured to contain 250 mg of mefloquine base and E555 to contain 250 mg of mefloquine·HCl. The administered dose was 4 tablets in both cases resulting in a total dose of 1100 mg for A and 1000 mg for B of mefloquine·HCl. These were the values employed in the subsequent data analysis.

Details of volunteer selection, drug administration and the blood sampling schedule for drug assays are described in the Final Clinical Report, Experiment Number 10, Bio-Med Inc. (January 9, 1979), a copy of which is appended (Appendix I). Whole blood concentrations of mefloquine were determined by a high pressure liquid chromatographic method reported previously.<sup>3</sup>

Compliance with the schedule of blood samples for drug assay was excellent for all of the 12 volunteers who completed the study. The exact sampling times and drug concentrations for each participant are presented in Appendix II.

#### Data Analysis

These data were evaluated in a number of different ways to compare the rate and relative extent of systemic absorption from the two formulations. Non-linear curve fitting to standard pharmacokinetic models\* was performed in a Tektronix 4052 Graphics Computer System with programs developed in the Division of Experimental Therapeutics, Walter Reed Army Institute of Research and later modified in the Division of Clinical Pharmacology, Department of Medicine, Duke University. Statistical analyses were performed using the Statistical Analysis System (SAS) at the University of North Carolina.

A simple comparison of the peak concentrations of mefloquine (Table I) was made using the analysis of variance (ANOVA) for a cross-over design with terms in the model for treatment, subject and serial effects. These peak concentrations were corrected according to the dose administered (A=100 mg, B=1000 mg) but not for body weight or estimated residual following the first dose.

A similar comparison of the areas under the concentration-time curve following each formulation was made. In this case the areas were calculated by the trapezoidal rule from time 0 to the final measured sample plus the extrapolated terminal portion of the curve based on a single exponential regression of the points on the curve beyond 96 hours. In addition, the area under the second concentration-time curve (Period 2) in each case was corrected by subtracting the extrapolated area under the first curve beyond the time of the second dose (i.e., residual area from Period 1). The plotted time concentration data and fitted terminal exponential regression in each case are shown in Appendix III.

From the areas thus estimated an apparent clearance term was calculated by dividing the area into the dose administered in each case:

$$Cl_{app} = \frac{D}{\text{Area}}$$

These clearance terms, shown in Table 3, were then compared by ANOVA for a cross-over design. Based on the assumption that the volume of distribution ( $V_d$ ) and elimination rate ( $Ke_l$ ) of mefloquine is the same regardless of the formulation in which it is administered, and the following relationship:

$$Cl_{app} = Ke_l \cdot V_d$$

significant apparent differences in clearance between the two formulations are directly attributable to differences in fractional absorption ( $F$ ).

Finally, all of the concentration-time data following administration of both formulations were fitted for each participant to a model which assumed that the volume of distribution and elimination rate constants for both formulations were the same but that the absorption rate constant and fractional absorption could vary independently. The parameters of this model, therefore, were:

$V$  = Volume of distribution  
 $\text{kel}$  = Elimination rate constant  
 $\text{ka}_1$  = Absorption rate constant for B (i.e., E555)  
 $\text{ka}_2$  = Absorption rate constant for A (i.e., HLR)  
 $F_1$  = Fractional absorption for B (E555)  
 $F_2$  = Fractional absorption for A (HLR)

The clearance terms (see Table 4) thus obtained were similarly compared by ANOVA for a cross-over design, again to test indirectly the hypothesis that  $F_1 \neq F_2$ . In addition, the mean ratio of  $F_1/F_2$  was calculated and its significance from unity tested by a one-sample t-test. The mean ratio of  $F_1/F_2$  was similarly calculated. Means of total fitted curves are shown for each individual in Appendix IV.

### Results

The corrected peak concentrations of each drug over following formulation A (HLR) and B (E555) are shown in Table 1. The ANOVA comparing these values (Appendix V) shows a significant difference among subjects ( $p < 0.05$ ) but no significant period effect ( $p > 0.54$ ). There was also a significant treatment difference in mean concentrations ( $p < 0.01$ ) favoring formulation A.

MEAN 34 1.083  
SD 15-0.5

The clearance terms computed from areas obtained by the trapezoidal rule plus exponential extrapolation of terminal points were similarly compared. These corrected clearance terms for each formulation are shown in Table 3. The ANOVA comparing these values (Appendix VI) shows a significant difference among subjects ( $p=0.0025$ ), no significant period effect ( $p=0.9229$ ) and a significant difference between treatments ( $p=0.0150$ ) favoring a higher fractional absorption for formulation A.

The fitted curves (see Appendix VII) provided a set of parameter estimates for each participant including an elimination rate constant from which the half-life was calculated. These values are shown for each subject in Table 4. The mean half-life in these 10 volunteers was approximately 12 days which corresponds well with previously reported results.<sup>5</sup> The clearance terms computed from the fitted curves are shown in Table 5. The ANOVA for these values (Appendix VIII) similarly shows a significant difference among subjects ( $p=0.0011$ ), no significant period effect ( $p=0.1184$ ), and a significant difference between treatments ( $p=0.0144$ ), again favoring a higher fractional absorption for formulation A.

The values for the absorption rate constants  $K_a$  estimated independently for each formulation and their ratio (formulation A/formulation B) are shown in Table 6. The mean ratio was 1.5589 and was significantly greater than 1.0 ( $p=0.009$ ).

The values for distribution coefficient as a function of the volume of distribution ( $\phi$ ) are shown in Table 7 based on the assumption that the volume of distribution for each drug is the same regardless of the formulation in which it is administered. The ratio of fractional absorption of the two forms

ulations (A/B) can be obtained by dividing these terms. The mean ratio was 1.3735 and was significantly greater than 1.0 ( $p=0.0012$ ).

### Conclusions and Discussion

Analyses of the blood concentration-time data from this comparative oral bioavailability study, by a variety of statistical and pharmacokinetic models, all indicate that the HLR tablet formulation containing 250 mg of mefloquine base was more rapidly and completely absorbed than was the Lafayette Pharmaceutical E555 tablet formulation containing 250 mg of mefloquine-HCl. Corrections were made in these analyses for the difference in dose (1000 mg versus 500 mg of the HCl salt), but not for differences in body weight of the individual participants. There is some controversy about whether or not such a correction should also be made, but in this case a correlation analysis of the parameter of interest (clearance) with body weight of the individual participants showed that no such correlation existed (coefficient correlation,  $-0.01$ ,  $p=0.1217$ ).

In a previous comparative bioavailability study formulation E443, which was also manufactured by Lafayette Pharmaceutical and was identical to the present E555, was compared with Interf formulation 8512. The latter was more rapidly and possibly more completely absorbed. Prior clinical use of the E443 formulation had been the case with E555. Since the HLR formulation was found to result in significantly higher peak blood concentrations of mefloquine with more rapid and complete absorption of the drug than does the E555 formulation, a higher than expected frequency of adverse experiences may be observed with clinical use of the HLR formulation.

The methods employed in this comparative oral bioavailability study demonstrate that it is not absolutely essential to allow sufficient time to elapse between doses to reach nondetectable blood concentrations of the drug. In the case of a drug like mefloquine, with a half-life greater than 10 days, this would clearly be impractical. It is nevertheless quite possible to compare the fractional absorption of two formulations.

## TABLE 1

A = HLR tablets 250 mg mefloquine base  
 B = E555 tablets 250 mg mefloquine-HCl

<u>Volunteer #</u>	<u>Period 1</u>	<u>Period 2</u>
261	B	A
262	A	B
263	A	--
264	B	A
265	B	A
266	B	A
267	A	B
268	A	B
269	A	B
270	A	B
271	B	A
272	B	A
273	B	A

Note: There are five individuals with sequence AB and seven with BA. The cross-over is, therefore, unbalanced.

TABLE 2

Peak Concentration (μg/ml) of Mefloquine  
(Corrected to 1000 mg Dose)

<u>Subject</u>	<u>FORMULATION</u>	
	<u>A</u>	<u>B</u>
261	0.737	0.383
262	0.750	0.802
264	1.229	0.628
265	1.054	0.928
266	0.811	0.611
267	1.211	1.025
268	0.636	0.498
269	0.623	0.678
270	0.629	0.403
271	0.932	0.873
272	0.838	0.312
273	0.957	0.615

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TABLE 3

Total Body Clearance of Mefloquine  
 Dose Divided by Area Under Concentration-Time Curves by Trapezoidal Rule  
 and Extrapolation of Single Exponential Fit of Terminal Data  
 (beyond 96 hours)

<u>Subject</u>	<u>FORMULATION</u>	
	<u>A</u>	<u>B</u>
261	3.339	5.283
262	3.607	3.307
264	1.274	2.168
265	2.297	3.067
266	3.887	4.407
267	1.338	2.292
268	4.391	5.252
269	3.585	3.930
270	5.195	1.574
271	3.777	4.152
272	3.825	4.287
273	4.119	5.117

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TABLE 4

<u>Subject</u>	<u>Kel</u>	<u><math>t_{\frac{1}{2}}</math> (days)</u>
261	0.001531	18.86
262	0.002065	13.99
264	0.001410	20.48
265	0.002403	12.02
266	0.002219	13.02
267	0.001539	18.77
268	0.002559	11.29
269	0.002192	13.18
270	0.005061	5.68
271	0.003021	9.00
272	0.003004	9.61
273	0.003768	<u>7.66</u>
Mean		11.96

TABLE 5

Total Body Clearance (ml min)  
 Obtained from Fitted Regression Curves:  
 Bicexponential Model

<u>Subject</u>	<u>Formulation</u>	
	<u>A</u>	<u>B</u>
261	3.158	4.582
262	2.940	3.653
264	1.658	2.497
265	1.633	3.495
266	1.761	3.316
267	1.735	1.525
268	1.342	1.305
269	1.713	3.493
270	1.347	1.351
271	1.454	1.352
272	1.148	1.516
273	1.373	1.511

TABLE 6

## Absorption Rate Constants

Subject	Formulation		Ratio A/B
	A	B	
261	0.1690	0.1516	1.1148
262	0.3892	0.2137	1.8212
264	0.4952	0.5382	0.9201
265	0.2603	0.2579	1.0093
266	0.3291	0.1408	2.3374
267	0.2303	0.1240	1.8573
268	0.2228	0.1842	1.2096
269	0.1735	0.0958	1.8111
270	0.4068	0.3208	1.2681
271	0.2565	0.2118	1.2110
272	0.2678	0.3250	0.8240
273	0.2469	0.0725	<u>3.4223</u>
Mean			1.5589

TABLE 7  
Ratio of Fractional Absorption

Subject	Formulation		Ratio
	A	B	
261	0.4848	0.3341	1.4511
262	0.7024	0.5653	1.2425
264	0.9049	0.5647	1.6024
265	0.9126	0.6875	1.3274
266	0.5900	0.5666	1.0413
267	0.6624	0.6094	1.1052
268	0.4343	0.4068	1.0712
269	0.5871	0.5489	1.0692
270	0.5647	0.3540	1.5952
271	0.5684	0.5226	1.1342
272	0.5395	0.5105	1.0648
273	0.7764	0.6213	1.2663
Mean			1.3735

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APPENDIX I

Final Clinical Report  
Experiment Number 10  
Bio-Med Inc.  
January 9, 1979

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TITLE:

COMPARATIVE BIOAVAILABILITY  
AND PHARMACOKINETICS OF  
WR 142,490-HCl (MEFLOQUINE  
HYDROCHLORIDE) AND MEFLOQUINE  
HYDROCHLORIDE-HLR

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## FINAL REPORT

### EXPERIMENT NUMBER 10

#### COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF WR 142,490-HCl (MEFLOQUINE HYDROCHLORIDE) AND MEFLOQUINE HYDROCHLORIDE-HLR

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## FINAL CLINICAL REPORT

### EXPERIMENT NUMBER 10

#### COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF WR 142,490·HCl (MEFLOQUINE HYDROCHLORIDE) AND MEFLOQUINE HYDROCHLORIDE·HLR\*

#### ABSTRACT

Mefloquine hydrochloride, a substituted quinoline methanol, has been shown to be an effective single dose agent in the treatment of chloroquine-resistant *P. falciparum* malaria and effective for prophylaxis. The drug administered to human subjects in single doses up to 1000 mg was well tolerated. Intolerance at higher doses was manifested by temporary light-headedness, diarrhea, abdominal cramps, occasional nausea and/or vomiting. Symptoms were considered dose related and mild in all cases.

A variety of formulations have been used in previous tolerance and therapeutic studies. Clinical results in infected volunteers and blood level determinations in a limited number of pharmacokinetic studies indicate considerable variation in the bioavailability of these formulations. The use of a new formulation in field studies, such as the HLR formulation, must therefore be supported by prior demonstration of adequate bioavailability.

A study for comparative bioavailability of the HLR formulation and an established effective formulation, WR 142,490·HCl, was done. A classical two way balanced crossover design including 3 groups of 4 subjects each was used. Symptoms were absent or mild and temporary. Symptomatology attributed to drug ingestion included gastrointestinal symptoms and headache following ingestion of both formulations. Lightheadedness occurred only following administration of the WR formulation. No significant changes in physical examination or laboratory values attributed to drug administration were observed. In conclusion, WR 142,490·HCl and the F. Hoffmann-La Roche, & Co. formulation were both well tolerated under conditions of this study. Drug assay analysis is not yet available and will be reported separately at a later date by the responsible institution.

\*F. Hoffmann-La Roche, & Co.

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## FINAL REPORT

### EXPERIMENT NUMBER 10

#### COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF WR 142,490·HCl (MEFLOQUINE HYDROCHLORIDE) AND MEFLOQUINE HYDROCHLORIDE·HLR\*

##### INTRODUCTION:

Mefloquine hydrochloride, a substituted quinoline methanol, has been shown to be an effective single dose agent in the treatment of chloroquine-resistant *P. falciparum* malaria. Its prophylactic effectiveness against chloroquine-resistant *P. falciparum* malaria inoculated by infected mosquitoes has also been demonstrated. Clinical studies in humans showed that 10 subjects who received 250 mg of WR 142,490·HCl weekly for 8 weeks were protected when exposed to mosquitoes heavily infected with multi-drug-resistant *P. falciparum*. The drug administered to human subjects in single doses up to 1000 mg was well tolerated. Intolerance at higher doses was manifested by temporary light-headedness, diarrhea, abdominal cramps, occasional nausea and/or vomiting. Symptoms were considered dose related and mild in all cases.

In addition, 12 healthy young males have completed a year long study during which each subject received a single weekly dose of 500 mg of WR 142,490·HCl without significant adverse clinical or laboratory effects. It appears that this antimalarial is well tolerated and deserving of additional clinical investigations in man.

A variety of formulations have been used in previous tolerance and therapeutic studies. Clinical results in infected volunteers and blood level determinations in a limited number of pharmacokinetic studies indicate considerable variation in the bioavailability of these formulations. The use of a new formulation in field studies (such as the HLR formulation) must therefore be supported by prior demonstration of adequate bioavailability.

This study was designed to compare specific bioavailability parameters of WR 142,490·HCl and the HLR preparation of Mefloquine·HCl following single oral dose administration to healthy human male subjects, i.e.: peak blood levels, time to peak level, blood level-time patterns and area under concentration-time curve.

\*HLR and WR as used in the text designate the F. Hoffmann-La Roche, & Co. and Walter Reed preparation respectively. Following a code number the letters designate the preparation administered.

The IND with Supplements and Clinical Summary were available at all processing committee meetings and were available at all times in the Office of the Clinical Director of BIO-MED, Inc.

METHODS AND MATERIALS:

Methods Subject Selection - Acceptability Criteria:

Thirteen healthy male subjects, 21 to 38 years of age, weighing 56-87 kg and within 10% of their ideal body weight, were employed for the study. They were recruited from the Washington, D.C. metropolitan area. Candidates were hired by BIO-MED, Inc. as temporary employees for study purposes.

Candidates for employment were screened to obtain the subjects for study. The medical evaluation included a comprehensive history and physical examination, chest X-ray, electrocardiogram, urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, and G6PD.

Subject acceptability criteria are based upon the precept that the risks of participation should be slight, and comparable for all subjects. Following this guideline, certain subjects were rejected routinely: for example, subjects with organic heart murmurs, splenomegaly or active lesions on chest X-ray. The presence of conditions which did not increase risk or potentially compromise the validity of the study, as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes, was not ordinarily cause for rejection. Deviations of laboratory values of 3 standard deviations or more from the mean were generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum sodium of 153 mEq/L of itself would not be a cause for rejection, whereas a serum calcium of 11.2 mg/dl would.

Whenever doubt existed concerning the eligibility of a subject a decision was made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner, questionable candidates were given full consideration and the integrity and ethics of the Research Team protected.

Qualified candidates were presented with a complete explanation of the background and procedures to be used in the study and all details of the protocol as it involved the individual subjects. They were interviewed in a group and individually in the presence of an investigator and a member of the Human Use Committee. Each participant was given the opportunity to ask questions. Following this, the consent form was read and those wishing to participate signed it in the presence of a witness, an investigator and a member of the Human Use Committee.

During the first 5 days of each study interval the subjects were housed in a controlled environment on Nursing Unit 5-W at the Washington Hospital Center. Thereafter, they reported according to the protocol schedule (page 4).

Subject Assignment - Drug Administration:

A classical 2 way balanced crossover design was used. Each subject was randomly assigned to 1 of 2 possible sequences of drug administration, within the limitations of the design.

Three groups of 4 subjects each were admitted to the study sequentially. Within each group the 2 formulations were administered at a dose of 4 tablets\* to 2 subjects each, by random assignment. Following a "wash out" period of 4 weeks, each subject was given 4 tablets\* of the alternate formulation. Follow-up and sampling times following each administration are listed in the tables on page 11.

On the day of drug administration, subjects were permitted to drink water ad lib until 1 hour prior to and 2 hours after drug administration. Breakfast was withheld. The drug was administered in the presence of a member of the investigating team. Subjects returned to a regular diet 6 hours after drug administration.

The clinical and laboratory evaluation of the subjects is outlined on the following page:

\*The 4 tablets for the Walter Reed formulation constituted a single dose of 1000 mg of Mefloquine·HCl, and for the F. Hoffmann-La Roche, & Co. preparation a single dose of 1100 mg Mefloquine·HCl. WR Lafeyette Pharmacal lot number E-555; HLR lot number 21-5998-001-01.

SCHEMATIC STUDY PLAN FOR EACH DOSING

STUDY DAY	0*	1*	2*	3*	4*	5	7	8	14	21
Dose			X							
Physical Exam	X		X				X			X
Interview	X	X	X	X	X		X			X
Vital Signs	X	X	X	X	X		X			X
ECG	X		X				X			X
Laboratory Tests <sup>+</sup>	X		X	X			X			X
Drug Assay <sup>++</sup>		X	X	X	X	X	X	X	X	X

\*Controlled Environment in Study Unit 5-W.

<sup>+</sup>Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Uric Acid, Total Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alkaline Phosphatase, SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies were done as clinically indicated.

<sup>++</sup>Drug Assay - Blood drawn on each subject immediately prior to drug administration and after dosing at 1,2,4,6,8,10,11, 12, 13, 15, 20, 24, 28, 34, 48, 56, 63, 72, 76, 80 hours and on days 5, 7, 8, 14, and 21.

The schedule for hematologic and biochemical blood tests is indicated. For these tests 27 ml venous blood was obtained while the subject was fasting before breakfast. Seven ml blood was used for determination of white blood cell and differential count, red blood cell count, hematocrit, hemoglobin, MCH, MCHC, MCV, and platelet count. Twenty ml of the venous blood specimen was centrifuged and the serum separated. The serum was divided into 2 samples. One sample was stored in the refrigerator as a "back-up" until the biochemical lab report was received. Thereafter it was stored in the freezer until released by the investigator. The other sample was used on the day obtained to determine the values for serum glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, and total bilirubin.

On the last study day for each subject final physical and laboratory evaluation was done. All abnormal findings caused follow-up until normalcy, stabilization, or proper medical disposition was secured.

Drug Assay Specimen Collection and Time Schedule:

Specimen collection for drug assay was as follows: 6 ml venous blood was obtained in a heparin rinsed syringe. It was placed in 16 x 125 mm glass test tubes with screw-on teflon lined caps. Specimens were stored at -20°C pending transport to Department of Pharmacology, Walter Reed Army Institute of Research, for drug assay. A Specimen Collection Worksheet (BMI-WS-1) was completed by the staff nurse on each subject participating in the study. Twenty-four hour urine specimens were collected for drug assay on days 0, 1, and 2 from 8:01 a.m. to 8:00 a.m. (See the tables and Specimen Collection Worksheet on pages 11 and 12 respectively.)

RESULTS:

Subject code no. 263 withdrew from the study before administration of the WR preparation. Subject code no. 273 was substituted and the sequence of drug administration was inadvertently reversed.

Symptoms:

All symptoms are tabulated in Table I (pages 18 through 20). Three subjects (code nos. 265, 268, and 270) had symptoms possibly drug related following administration of each formulation. Four subjects (code nos. 261, 264, 266, and 271) had symptoms only after ingestion of the HLR preparation and 2 subjects (code nos. 262 and 272) only following administration of the WR formulation. Therefore, 7 of 13 administrations of the HLR formulation and 5 of 12 administrations of the WR preparation were associated with minor, possibly drug related symptoms.

Gastrointestinal:

The most frequent symptoms involved the gastrointestinal tract. Nausea variously described as a "queasy" feeling and "stomach ache" was associated with the administration of the HLR formulation on 2 occasions (subject code nos. 264 and 265) and the WR formulation on 3 occasions (subject code nos. 262, 265, and 268). Two other subjects receiving the HLR preparation had nausea not attributed to drug: 4 days after ingestion of the HLR preparation, subject code no. 262 had nausea

with 2 episodes of emesis. He was anorexic and dysphoric for approximately 1 week. Subsequently, a severe dental infection and abscess was found which was considered causal. Subject code no. 268 had transient lightheadedness and nausea associated with bloodletting 20 hours after administration of the HLR preparation not considered drug induced.

Loose stools occurred in seven subjects. Four subjects (code nos. 261, 265, 268, and 271) only following administration of the HLR preparation and 2 only following administration of the WR formulation. One subject had loose stools after receiving each formulation. Three subjects had onset of loose stools within 2 hours of drug administration: subject code nos. 261 and 268 after HLR and subject code no. 272 after the WR formulation. For subject (code no. 271) having 2 loose stools on the day of administration of the HLR preparation, the time of onset was not documented. One subject (code no. 266) had 1 loose stool 8 hours after receiving the WR formulation. Another subject (code no. 265) had 1 watery stool 48 hours after ingesting the HLR preparation. In 2 subjects with recurrent loose stools (code nos. 268 HLR and 270 WR) the frequency was 1 to 3 per day and the duration was 6 days except that subject code no. 268 HLR had abdominal cramps and passed 7 watery stools during the first 12 hours after onset at 45 minutes after dosing. In all other subjects the duration was of less than 24 hours or (code no. 265) only 1 loose stool was evacuated. The passage of watery stools was not associated with abdominal cramps except at onset in 1 subject (code no. 268 HLR).

In summary, 12 of 25 drug administrations were associated with mild, non-incapacitating gastrointestinal symptoms potentially attributable to drug administration: 7 episodes following HLR and 5 episodes following WR formulation administration.

#### Neurologic:

Eight of 25 drug administrations were associated with headache, lightheadedness, syncope, vasovagal reactions, or nightmares. However, only 2 subjects had symptoms considered potentially drug related: subject code no. 265 had headache and lightheadedness following administration of the HLR and WR formulation respectively. Additionally, subject code no. 268 had both symptoms only after receiving the WR preparation. Potentially drug related lightheadedness occurred as follows: subject code no. 265 WR noted onset of vague "dizziness" 4 hours after dosing with duration of 9 hours. The other subject with lightheadedness (code no. 268 WR) had been typing and reading constantly. Seven hours after dosing, he noted headache, lightheadedness, and nausea of 3 hours duration dissipating rapidly upon discontinuation of typing and reading.

Light-headedness not attributed to drug administration occurred on 3 occasions. Subject code no. 273 experienced light-headedness and syncope associated with bloodletting 30 minutes before dosing. Similarly, 2 subjects (code nos. 268 HLR and 272 WR) experienced transient vasovagal reactions associated with bloodletting 20 and 15 hours after dosing, respectively.

Three subjects in addition to subject code no. 268 WR noted headaches. One subject (code no. 265 HLR) experienced a possibly drug related headache. He noted onset of a mild right temporal headache 6 hours after dosing which persisted for 8 hours. Two other subjects had headaches not attributable to drug: 1 subject (code no. 261 WR) had a mild right temporal headache starting prior to dosing, of less than 24 hours duration. The other subject (code no. 263 HLR) had onset of a mild headache of approximately 15 minutes duration 6 days after dosing. These latter 2 subjects stated the headaches were similar to those they experienced commonly without obvious precipitants.

One subject (code no. 268 HLR) had vivid dreams and nightmares possibly but not probably drug related starting 56 hours after dosing and recurring nightly for 4 nights.

In summary, 1 subject (code no. 268) had dizziness, headache, and nausea of 3 hours duration with onset 7 hours after receiving the WR formulation, possibly precipitated or aggravated by typing and reading. Another subject (code no. 265) had vague "dizziness" for approximately 9 hours starting 4 hours after receiving the WR preparation. The same subject had a mild right temporal headache of approximately 8 hours duration starting 6 hours after receiving the HLR formulation. In both subjects the neurologic symptoms potentially drug related were mild and temporary. Neurologic symptoms otherwise were not considered potentially drug related.

#### Miscellaneous:

Three subjects (code nos. 264, 272, and 273) had symptoms of the common cold during the interval of study. Three other subjects (code nos. 262, 267, and 268) had symptoms and signs not considered related to drug administration which are presented in Table I and the individual subject final summaries.

#### Physical Findings:

No changes attributed to drug administration occurred in any subject.

Laboratory Values:

The range ( $\bar{x} \pm 2$  SD) of laboratory values for the BIO-MED, Inc. normal population ( $n > 100$ ) is presented as Table IIA (page 21). All laboratory values outside the normal range are included in Table IIB (pages 22 through 24). All subjects had 2 or more values outside the normal range reported. Minimal serum carbon dioxide content elevation reported in 9 subjects was the most frequently reported abnormality. The elevations were minimal and inconsistent, occurring before and after administration of both formulations without discernable pattern. This observation of minimal, inconsistent deviations of laboratory values in a random manner is characteristic of most of the abnormalities reported and not considered drug related. In some subjects values for a given determination clustered about the upper or lower limits of the range for that determination. Subject code no. 264 exemplifies this occurrence for serum creatinine and albumin values. Subject code no. 273 demonstrated a persistent minimal elevation of serum alkaline phosphatase before and after administration of both formulations. In the absence of other laboratory or clinical findings to suggest an active disease process, the observation of a fixed pattern of deviation before and after drug administration is not considered drug related.

Two subjects (code nos. 261 and 266) demonstrated minimal SGPT elevations following administration of the HLR formulation: an isolated elevation to 56 U/L occurred 6 days after dosing in subject code no. 261 and elevations to 52 U/L and 48 U/L occurred 2 and 20 days after dosing respectively in subject code no. 266 with a normal value of 38 U/L reported 6 days after dosing. The upper limits for this determination is 47 U/L. These minimal and inconsistent deviations may be considered possibly, but not probably drug related.

Electrocardiograms:

No significant changes in serial rhythm tracings occurred in any subject.

DISCUSSION:

The 2 formulations of mefloquine were well tolerated at the dose levels administered. Five of 12 administrations of the WR formulation and 7 of 13 administrations of the HLR preparation were associated with symptoms. Three subjects had symptoms following administration of each drug, four only associated with the HLR formulation, and 2 only associated

with the WR preparation. The character and frequency of symptoms suggest no significant difference in clinical response to the 2 formulations. Therefore, symptoms potentially drug related occurred in 13 of the 25 trials. The symptoms were mild and did not interfere with normal activity.

The absence of gastrointestinal symptoms in previous WR 142,490·HCl safety and tolerance studies at comparable dose levels suggests their frequency in the current study may be attributed in part to the requirements of the experimental protocol. The subjects in this study ingested the drug following an overnight fast and continued to fast for 6 hours following drug administration. During this interval frequent bloodletting was required for specimen collection. These factors may have been causal or contributory to the gastrointestinal symptomatology described.

Light-headedness, headache, and nightmares were observed in association with WR 142,490·HCl administration in previous studies at dose levels higher than those administered in this study. Their frequency in this study was 3 potentially drug related involving 2 subjects in 25 trials: 2 after administration of the WR formulation and 1 after administration of the HLR preparation. The symptoms were mild, temporary, and not incapacitating. The conditions of the study rather than drug effect may have been causal or contributed to the neurologic symptoms.

Intercurrent illnesses and medical conditions unrelated to drug administration occurred with the frequency expected in a study of this duration.

Similarly deviations of laboratory values not attributable to drug administration were frequent. Two subjects receiving the HLR preparation had minimal elevation of SGPT values reported considered possibly, but not probably drug related.

In summary, the study has been completed without significant deviations or adverse reactions and the specimens for assay are in custody of the responsible organization.

CONCLUSIONS AND RECOMMENDATIONS:

This study was performed for pharmacokinetic purposes. Noted as an integral part of monitoring was the occurrence of mild and temporary gastrointestinal and neurologic symptoms considered related primarily to prolonged fasting and frequent bloodletting.

The drug assay results will be reported at a later date by the responsible organization.

EXPERIMENT 10: COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF  
OF WR 142,490·HCl (MEFLOQUINE HYDROCHLORIDE) and  
MEFLOQUINE HYDROCHLORIDE·HLR

DRUG ASSAY COLLECTION

DAY OF THE STUDY	SPECIMEN NUMBER	BLOOD SPECIMEN TIME	BLOOD VOLUME (ml)
1	1	0 Prior to dosing	6
	2	1 hr 9:00 AM	6
	3	2 hr 10:00 AM	6
	4	4 hr NOON	6
	5	6 hr 2:00 PM	6
	6	8 hr 4:00 PM	6
	7	10 hr 6:00 PM	6
	8	11 hr 7:00 PM	6
	9	12 hr 8:00 PM	6
	10	13 hr 9:00 PM	6
	11	15 hr 11:00 PM	6
2	12	20 hr 4:00 AM	6
	13	24 hr 8:00 AM	6
	14	28 hr NOON	6
	15	34 hr 6:00 PM	6
3	16	48 hr 8:00 AM	6
	17	56 hr 4:00 PM	6
	18	63 hr 11:00 PM	6
4	19	72 hr 8:00 AM	6
	20	76 hr NOON	6
	21	80 hr 4:00 PM	6
<u>HOME</u>			
5	22	96-98 hr 8:00-10:00 AM	6
7	23	144-146 hr 8:00-10:00 AM	6
8	24	168-170 hr 8:00-10:00 AM	6
14	25	312-314 hr 8:00-10:00 AM	6
21	26	480-482 hr 8:00-10:00 AM	6
			TOTAL 156 (ml)

URINE SPECIMENS

0	1	8:01 AM to 8:00 AM
1	2	8:01 AM to 8:00 AM
2	3	8:01 AM to 8:00 AM

TOTAL AMOUNT OF BLOOD WITHDRAWN FOR EACH STUDY SUBJECT  
FOLLOWING EACH DRUG ADMINISTRATION

DAY	HEMATOLOGY	CHEMISTRY	BLOOD ASSAY	TOTAL (ml)
0	7	20		27
1			66	66
2	7	20	24	51
3	7	20	18	45
4			18	18
5			6	6
7	7	20	6	33
8			6	6
14			6	6
21			6	6
			TOTAL 264 (ml)	

### Specimen Collection Worksheet

Experiment #10: COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF  
WR 142,490·HCl (MEFLOQUINE HYDROCHLORIDE) AND  
MEFLOQUINE HYDROCHLORIDE·HLR

Name: \_\_\_\_\_ Code: \_\_\_\_\_ Age: \_\_\_\_\_ Ht: \_\_\_\_\_ cm. Wt: \_\_\_\_\_ k.

## First Dosing

### Drug Formulation:

Total Dose: mg Dose (mg/kg):

Date & Time Dosed:

### Second Dosing

### Drug Formulation:

Total Dose: mg Dose (mg/kg):

Date & Time Dosed:

### Whole Blood Collection

Spec. No.	P. D. *	Sched	Actual
1	-15 min.		
2	1 hr		
3	2 hr		
4	4 hr		
5	6 hr		
6	8 hr		
7	10 hr		
8	11 hr		
9	12 hr		
10	13 hr		
11	15 hr		
12	20 hr		
13	24 hr		
14	28 hr		
15	34 hr		
16	48 hr		
17	56 hr		
18	63 hr		
19	72 hr		
20	76 hr		
21	80 hr		
22	96-98 hr		
23	144-146 hr		
24	168-170 hr		
25	312-314 hr		
26	430-482 hr		

### Whole Blood Collection

Spec. No.	P. D. *	Sched	Actual
1	-15 min.		
2	1 hr		
3	2 hr		
4	4 hr		
5	6 hr		
6	8 hr		
7	10 hr		
8	11 hr		
9	12 hr		
10	13 hr		
11	15 hr		
12	20 hr		
13	24 hr		
14	28 hr		
15	34 hr		
16	48 hr		
17	56 hr		
18	63 hr		
19	72 hr		
20	76 hr		
21	80 hr		
22	96-98 hr		
23	144-146 hr		
24	168-170 hr		
25	312-314 hr		
26	480-482 hr		

#### 24 Hr. Urine Collections

STUDY DAY	TIME		TOTAL		Vol (ml)
	Begin	End	Hrs.	Min.	
0	+	0800			
1	0801	0800			
2	0301	0800			

#### 24 Hr. Urine Collections

24 HR. URINE COLLECTIONS					
STUDY DAY	TIME		TOTAL		Vol (ml)
	Begin	End	Hrs.	Min.	
0	+	0800			
1	0801	0800			
2	0801	0800			

\* Post Dose

+Variable fraction of 24 hour collection due to starting times.

BMI-WS-1

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## EXPLANATION FOR POTENTIAL SUBJECTS ANTIMALARIAL DRUG PROJECT EXPERIMENT NUMBER 10 Comparative Bioavailability and Pharmacokinetics of WR 142,490-HCl (Mefloquine Hydrochloride) and Mefloquine Hydrochloride-HLR

### GENTLEMEN:

This document explains the nature of the study, its purpose, procedures, risks and benefits. You will be given the opportunity after reading it to ask additional questions. If you then choose to participate as a research subject, you will be asked to initial the last page signifying that you have read and understand its contents prior to obtaining your formal written consent to participate in the study. The subject will participate for a total of 50 days.

This study involves taking by mouth the drug mefloquine hydrochloride. Mefloquine is similar to quinine and has been approved by the Food and Drug Administration for investigational studies. The drug has been administered to more than 100 subjects to determine its safety and tolerance, and ability to prevent and cure malaria.

Previous studies with this drug established that it was well tolerated in single doses up to 1000 mg. Doses of 1250, 1500, and 1750 mg occasionally caused transient light-headedness or gastrointestinal symptoms. At 1250 mg only mild diarrhea lasting for  $\frac{1}{2}$  to 3 hours after taking the drug was reported. There was no associated nausea, vomiting or abdominal pain. At 1500 mg two subjects reported a transient sense of light-headedness, two subjects had mild diarrhea without other symptoms, and one subject vomited five minutes after taking the drug. At 1750 mg there was mild to moderate diarrhea, with the number of stools varying from 1 to 6 over a period of 35 minutes to 6 hours after taking the drug. Occasional nausea and mild abdominal cramps were also reported by some subjects.

This study is to compare the bioavailability of two different formulations. It will be conducted using one tablet formulation provided by Walter Reed Army Institute of Research, and the other provided by F. Hoffman-La Roche, & Co. The dose to be administered in both cases is 4 tablets\*. You may experience some of the symptoms discussed above. No other symptoms or long term effects are anticipated.

\*The four tablets for the Walter Reed formulation will constitute a single dose of 1000 mg of Mefloquine-HCl, and for the F. Hoffman-La Roche, & Co. preparation a single oral dose of 1100 mg Mefloquine-HCl.

We will study these two preparations by using a two way cross-over design. You will be assigned in a random manner to one of 3 groups designated Group I through III, each group containing 4 subjects. You will receive one drug preparation on one occasion and four weeks later the other formulation. You will be required to remain on the research unit for five days at the beginning of each period.

On the day the drug is to be administered, breakfast will be withheld. You will be permitted to drink water as you wish except for 3 hours encompassing the time of drug administration. The drug will be administered in the presence of a member of the investigating team at 8:00 AM. At 2:00 PM you may resume the normal diet you select from the hospital menu until you are discharged from the unit.

The purpose of the present study is to accurately determine the pattern in which the drug appears and disappears from your body. Blood (6 ml) will be drawn at the times specified in Table II after you take the drug to measure the amount of drug present. You will notice that the frequency of specimens is much greater during the early days of the study. In addition, we will collect all of your urine during the first 3 days encompassing the time of drug administration. You will be admitted to the research unit for the first 5 days and seen on brief visits for a period of 3 weeks. On the fourth week you will be readmitted to the research unit for a second 5 day period, after which you will be seen on brief visits thereafter per schedule. The long period of follow-up is required because of the expected slow release of the drug from the body. It is important that the blood be obtained as nearly as possible to the times specified in Table II and that you eat a light breakfast (i.e. cereal, milk, juice, coffee, bread -- no eggs or bacon) on the days you come in for blood drawing. It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol. Such factors as time of day, meals, alcohol, other drugs, and lack of proper sleep may affect the level of drug in your blood on any given day.

It is expected that the amount of drug remaining in your blood on the last day of the study will be very low. However, the late specimens are just as important as the early specimens in obtaining an overall accurate assessment of the way the drug is handled by the body. Therefore, please do not start the study if you anticipate difficulty in adhering to the schedule.

The amount of blood to be withdrawn for the entire study will be 555 ml, which is obtained over a seven week period and is about 39 ml more than a unit of whole blood that many people donate at American Red Cross Center Blood Banks. Instead of repeated venipunctures we will place a small teflon catheter in an arm vein and obtain the blood samples from it during the first fifteen (15) hours. In this way repeated venipunctures may not be necessary. The specifics for the study are presented in the schematic on the following page.

SCHEMATIC STUDY PLAN FOR EACH DOSING

DAY OF STUDY	0*	1*	2*	3*	4*	5	7	8	14	21
Dose			X							
Physical Exam	X			X				X		X
Interview	X	X	X	X	X		X			X
Vital Signs	X	X	X	X	X		X			X
ECG	X		X				X			X
Laboratory Tests <sup>+</sup>	X		X	X			X			X
Drug Assay <sup>++</sup>		X	X	X	X	X	X	X	X	X

\*Controlled Environment

<sup>+</sup>Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Uric Acid, Total Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alkaline Phosphatase, SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, and Urinalysis. Additional studies will be done as clinically indicated.

<sup>++</sup>Drug Assay - Each subject immediately prior to drug administration and after dosing at 1, 2, 4, 6, 8, 10, 11, 12, 13, 15, 20, 24, 28, 34, 48, 56, 63, 72, 76, 80 hours and on days 5, 7, 8, 14, and 21.

On the days indicated by \*, the participants in the study will remain in a controlled environment. The entire group will remain together with a member of the Research Unit Staff and will function according to their direction. Facilities provided while participating in the study include room and board with a study-lounge area. Recreation (tennis and basketball) is also provided if weather conditions permit and supervision is available.

You have already had many of the examinations listed on the schematic as a part of your qualification examination. The laboratory tests require urine collections and venipunctures to obtain blood specimens. This will not affect you except for temporary discomfort associated with obtaining blood from your arm vein.

On the last study day for each subject final physical and laboratory evaluation will be done. All abnormal findings will cause follow-up until normalcy, stabilization or proper medical disposition is secured.

The Human Use Committee members are also looking after your safety. They insure that you are not subjected to undue risk and discomfort. A member of this committee will be available to speak with you at the Washington Hospital Center. After members of the investigating team and Human Use Committee are satisfied that you understand the study and written informed consent form you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent you signify that the study has been explained to you with regard to its risks and requirements and you wish to participate.

It should be clear that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem, and to Americans, civilian and military, who may travel to these areas. For this reason especially, your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent at any time without prejudice.

If after reading this document, you have any additional questions, please ask them before affixing your initials below and signing the consent form.

Initials of Participant

SUBJECT AGREEMENT

CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, \_\_\_\_\_, hereby give my informed consent to participate as a study subject in the study entitled, "Comparative Bioavailability and Pharmacokinetics of WR 142,490-H (Mefloquine Hydrochloride) and Mefloquine Hydrochloride-HLR." \_\_\_\_\_

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. [redacted], and are set forth in the document entitled, "EXPLANATION: ANTIMALARIAL DRUG PROJECT EXPERIMENT NUMBER 10, Comparative Bioavailability and Pharmacokinetics of WR 142,490·HCl (Mefloquine Hydrochloride) and Mefloquine Hydrochloride·HLR," which I have signed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at any time; however, I may be requested to undergo further examination, if in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publications of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

Date \_\_\_\_\_ Witness - Human Use Comm. Cert. \_\_\_\_\_

**Signature** \_\_\_\_\_ **Investigator Certification** \_\_\_\_\_

Address \_\_\_\_\_ Witness \_\_\_\_\_

REAFFIRMATION OF CONSENT:

Witness

Date \_\_\_\_\_ Witness \_\_\_\_\_

Signature

EXPERIMENT NO. 10: COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF  
WR 142,490·HCl (MEFLOQUINE HYDROCHLORIDE) AND MEFLOQUINE HYDROCHLORIDE·HLR

TABLE I: SYMPTOMS SUMMARY

GROUP	CODE NUMBER	FORMULATION		Nausea		Loose Stool		Headache		Light-headedness		Other†
		1st Dose	2nd Dose	A*	B*	A	B	A	B	A	B	
I	261	HLR†				Watery stools x 3						
		WR†				2.0	1.5					
262		HLR	96.0	72.0				Right temporal -1.0	<24.0			Emesis x 2 108.0   122.0
		WR	1.0	5.0								Anorexic, dysphoria 96.0   168.0
263		HLR										Pale, hyperventilation, after shower: 54.0   0.3 Pain, dental abscess 336.0   192.0
		WR										
264		HLR						144.0   Chronic ≈ 0.15				
		WR						NOT DOSED				

\*A = Onset hours . minutes after dosing: (-) before dosing  
\*B = Duration hours . minutes after onset

†See Individual Subject Final Summary for details.

-HLR is designated as Formulation A  
-WR is designated as Formulation B

TABLE I: SYMPTOMS SUMMARY (cont.)

GROUP	CODE NUMBER	FORMULATION		Nausea		Loose Stool		Headache		Light-headedness		Other <sup>†</sup>
		1st Dose	2nd Dose	A*	B*	A	B	A	B	A	B	
II	265	HLR <sup>†</sup>	"Queasy stomach" -1.0	Watery stool x 1 48.0	< 0.05	Right temporal 6.0	8.0	"Dizziness" 4.0		"Dizziness" 4.0		B
		WR <sup>†</sup>	Stomach ache 3.30	≈ 0.20								
266		HLR						NO SYMPTOMS				
267		WR						NO SYMPTOMS				
268		HLR	2° to bloodletting 20.0	0.05	7 Day <sup>1</sup> , then 0.45	1-2 / day 144.0		2° to bloodletting 20.0		Vivid dreams, nightmares 56.0		Perianal pain - fissures ≈ 168.0
		WR	7.0	3.0 <sup>†</sup>				7.0	3.0 <sup>†</sup>	7.0	3.0 <sup>†</sup>	60.0
III	269	HLR						NO SYMPTOMS		NO SYMPTOMS		≈ 2.0

\*A = Onset hours . minutes after dosing: (-) before dosing

\*B = Duration hours . minutes after onset

<sup>†</sup>See Individual Subject Final Summary for details:

-HLR is designated as Formulation A  
-WR is designated as Formulation B

TABLE I: SYMPTOMS SUMMARY (cont.)

GROUP NUMBER	CODE NUMBER	FORMULATION	1st Dose	2nd Dose	Nausea		Loose Stool	Headache	Light-headedness	Other <sup>†</sup>
					A*	B*				
III	270	HLR <sup>†</sup>					Watery stool x 1 6.0 < 0.05			
			WR <sup>†</sup>				Recurrent 2-3x / day 6.0 144.0			
271		HLR					Watery stools x 2 unrecorded < 24.0			
			WR				NO SYMPTOMS			
272		HLR								
			WR				Recurrent x 2 1.0 2.0			
I	273	HLR								
			WR				NO SYMPTOMS			

\*A = Onset hours . minutes after dosing: (-) before dosing  
 \*B = Duration hours . minutes after onset

<sup>†</sup>See Individual Subject Final Summary for details:

-HLR is designated as Formulation A  
 -WR is designated as Formulation B

TABLE IIA: LABORATORY VALUES, NORMAL RANGE

April - June 1975

AMDP Subjects

Age: 21-45 Sex: Male Normal Population: n > 100  
Laboratory: National Health Laboratories

	$\bar{x}$	S.D.	$\pm 2$ S.D.
Glucose (mg/dl)	90	12	66-114
BUN (mg/dl)	15	3.1	9-21
Creatinine (mg/dl)	1.1	0.16	0.8-1.4
Sodium (mEq/L)	144	3.5	137-151
Potassium (mEq/L)	4.4	0.41	3.6-5.2
Chloride (mEq/L)	104	3.0	98-110
Carbon Dioxide (mEq/L)	27	1.9	23-31
Uric Acid (mg/dl)	6.0	1.0	4-8
Total Protein (g/dl)	7.2	0.41	6.4-8.0
Albumin (g/dl)	4.6	0.25	4.1-5.1
Globulin (g/dl)	2.6	0.42	1.8-3.4
Calcium (mg/dl)	10	0.44	9.0-10.9
Phosphate (mg/dl)	3.5	0.50	2.5-4.5
Cholesterol (mg/dl)	176	33	110-242
Triglyceride (mg/dl)	111	58	0-207
Alkaline Phosphatase (U/L)	60	17	26-94
SGOT (U/L)	23	12	0-47
SGPT (U/L)	17	15	0-47
LDH (U/L)	153	40	73-233
Total Bilirubin (mg/dl)	0.58	0.34	0.0-1.3
Hematocrit (Vol %)	45	2.52	40-50
Hemoglobin (GMS %)	15	0.84	13.3-16.7
WBC (thous/cu mm)	6.3	1.6	3.1-9.5
RBC (million/cu mm)	5.0	0.36	4.3-5.7
Lymph (%)	39	9.8	19-59
Seg. Neutrophils (%)	58	11	36-80
MCV (cu microns)	90	3.85	82-98
MCHC (%)	33	2.0	29-37
MCH (micro micro GM)	30	1.45	27-33
Platelet Count (thous/cu mm)	264	81	102-426

EXPERIMENT NO. 10: COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF  
WR 142,490-HCl (MEFLOQUINE HYDROCHLORIDE) AND MEFLOQUINE HYDROCHLORIDE-HLR

TABLE IIB: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES

GROUP- CODE NUMBER	FORMULATION		TESTS		FIRST DOSE STUDY DAY							SECOND DOSE STUDY DAY							NORMAL RANGE
	1st Dose	2nd Dose	Screen	0	2	3	7	0	2	3	7	0	2	3	7	21			
I- 261	WR <sup>†</sup>	HLR <sup>†</sup>	Glucose	97	105	107	119 <sup>*</sup>	97	96	103	124 <sup>*</sup>	108	92	66-114 mg/dl	220 <sup>*</sup>	39	0 - 207 mg/dl	0 - 47 U/L	
			Triglyceride	88	117	153	167	188	210 <sup>*</sup>	128	32	33	35	56 <sup>*</sup>	39	0 - 5 %	0 - 5 %	0 - 5 %	
			SGPT	40	37	35	30	42	5	2	3	7 <sup>*</sup>	3	3	4	4	4	0 - 5 %	
			Eosinophiles	5	2	4	5												
I- 262	HLR	WR	Carbon Dioxide	35 <sup>*</sup>	33 <sup>*</sup>	34 <sup>*</sup>	33 <sup>*</sup>	31	32 <sup>*</sup>	33 <sup>*</sup>	34 <sup>*</sup>	29	28	23 - 31 mEq/l					
			Total Protein	7.2	6.8	6.3 <sup>*</sup>	6.3 <sup>*</sup>	7.1	7.2	6.5	7.5	7.1	7.1	6.4 - 8.0 g/l					
			Albumin	4.6	4.3	3.9 <sup>*</sup>	4.0 <sup>*</sup>	4.5	4.2	4.0 <sup>*</sup>	4.6	4.4	4.4	4.1 - 5.1 g/l					
			White Blood Cell Count	6.7	5.4	7.3	6.8	11.0 <sup>*</sup>	6.2	5.8	5.9	6.8	11.2 <sup>*</sup>	3.1-9.5 th/c					
I- 263	HLR	-	Carbon Dioxide	28	30	29	28	32 <sup>*</sup>	-	-	-	-	-	-	23 - 31 mEq/l				
			Uric Acid	4.6	5.2	5.5	4.5	3.6 <sup>*</sup>	-	-	-	-	-	-	4 - 8 mg/dl				
			Albumin	4.3	4.0 <sup>*</sup>	4.2	4.2	4.2	-	-	-	-	-	-	4.1 - 5.1 g/l				
			Creatinine	0.7 <sup>*</sup>	0.7 <sup>*</sup>	0.5 <sup>*</sup>	0.6 <sup>*</sup>	0.6 <sup>*</sup>	0.6 <sup>*</sup>	0.6 <sup>*</sup>	0.5 <sup>*</sup>	0.5 <sup>*</sup>	0.5 <sup>*</sup>	0.5 <sup>*</sup>	0.8 - 1.4 mg/l	4.2	4.2	4.1 - 5.1 g/l	
I- 264	WR	HLR	Creatinine	0.7 <sup>*</sup>	0.7 <sup>*</sup>	0.5 <sup>*</sup>	0.6 <sup>*</sup>	0.6 <sup>*</sup>	0.6 <sup>*</sup>	0.6 <sup>*</sup>	0.5 <sup>*</sup>	0.5 <sup>*</sup>	0.5 <sup>*</sup>	0.5 <sup>*</sup>	0.8 - 1.4 mg/l				
			Albumin	4.2	4.2	3.8 <sup>*</sup>	4.1	4.1	4.5	4.4	4.0 <sup>*</sup>	4.3	4.4	4.4	4.2	4.2	4.1 - 5.1 g/l		
			Carbon Dioxide	33 <sup>*</sup>	29	35 <sup>*</sup>	33 <sup>*</sup>	33 <sup>*</sup>	30	34 <sup>*</sup>	32 <sup>*</sup>	32 <sup>*</sup>	34 <sup>*</sup>	34 <sup>*</sup>	23 - 31 mEq/l				
			Total Protein	6.5	6.5	6.5	6.0 <sup>*</sup>	6.4	6.6	6.8	6.4	6.6	6.5	6.4 - 8.0 g/l					
II- 265	WR	HLR	Albumin	4.2	4.3	4.2	4.1	4.0 <sup>*</sup>	4.1	4.3	4.5	4.1	4.2	4.1	4.1 - 5.1 g/l				
			Cholesterol	232	242	258 <sup>*</sup>	210	207	243 <sup>*</sup>	249 <sup>*</sup>	234	226	236	236	242 mg/dl				
			Alkaline Phosphatase	113 <sup>*</sup>	100 <sup>*</sup>	97 <sup>*</sup>	93	99 <sup>*</sup>	101 <sup>*</sup>	107 <sup>*</sup>	97 <sup>*</sup>	104 <sup>*</sup>	95 <sup>*</sup>	95 <sup>*</sup>	110 - 242 mg/dl				
			LDH	205	192	194	146	190	194	168	173	182	235 <sup>*</sup>	235 <sup>*</sup>	26 - 94 U/L				
II- 266	WR	HLR	Eosinophiles	1	0	2	1	3	1	6 <sup>*</sup>	2	0	0	0	0 - 5 %				
			Carbon Dioxide	31	27	31	31	30	28	27	27	29	32 <sup>*</sup>	32 <sup>*</sup>	23 - 31 mEq/l				
			SGPT	20	24	36	36	20	25	37	52 <sup>*</sup>	38	48 <sup>*</sup>	48 <sup>*</sup>	0 - 47 U/L				

\*denotes abnormality

<sup>†</sup>HLR is designated as Formulation A and WR as Formulation B in Individual Subject Final Summaries

TABLE IIB: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES (cont.)

\*denotes abnormality  
†HLR is designated as

Formulation B in Individual Subject Final Summaries

TABLE IIB: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES (cont.).

denotes abnormality  
ILR is designated as

## Individual Subject Final Summaries

APPENDIX II

Sample Times and Blood Concentrations  
of Mefloquine

PHSC 84-0083  
SW 15-8 18

Experiment #10

Deesak Bakhru 251 Age 21 Height 5'4" Wt 151 lbs

First-dose formulation B - Laffayette  
Dosed on 1/1/78 0015

Sample	Time Post-Dose	Actual Time	Code Dose Time
1	015 min	0805	00
	1 hr	0815	
2	1 hr	0925	57
3	1 hr	015	11
4	1 hr	020	105
5	1 hr	140	114
6	1 hr	1210	123
7	1 hr	1312	134
8	1 hr	1205	125
9	1 hr	0015	40
10	1 hr	0015	00
11	1 hr	0015	00
12	1 hr	0240	240
13	1 hr	0350	350
14	1 hr	0610	297
15	1 hr	1150	365
16	1 hr	0030	282
17	1 hr	0030	319
18	1 hr	0030	306
19	1 hr	0230	311
20	1 hr	0230	312
21	1 hr	0230	313
22	1 hr	0230	314
23	1 hr	0230	315
24	1 hr	0230	316
25	1 hr	0230	317
26	1 hr	0230	318
27	1 hr	0230	319
28	1 hr	0230	320
29	1 hr	0230	321
30	1 hr	0230	322
31	1 hr	0230	323
32	1 hr	0230	324
33	1 hr	0230	325
34	1 hr	0230	326
35	1 hr	0230	327
36	1 hr	0230	328
37	1 hr	0230	329
38	1 hr	0230	330
39	1 hr	0230	331
40	1 hr	0230	332
41	1 hr	0230	333
42	1 hr	0230	334
43	1 hr	0230	335
44	1 hr	0230	336
45	1 hr	0230	337
46	1 hr	0230	338
47	1 hr	0230	339
48	1 hr	0230	340
49	1 hr	0230	341
50	1 hr	0230	342
51	1 hr	0230	343
52	1 hr	0230	344
53	1 hr	0230	345
54	1 hr	0230	346
55	1 hr	0230	347
56	1 hr	0230	348
57	1 hr	0230	349
58	1 hr	0230	350
59	1 hr	0230	351
60	1 hr	0230	352
61	1 hr	0230	353
62	1 hr	0230	354
63	1 hr	0230	355
64	1 hr	0230	356
65	1 hr	0230	357
66	1 hr	0230	358
67	1 hr	0230	359
68	1 hr	0230	360
69	1 hr	0230	361
70	1 hr	0230	362
71	1 hr	0230	363
72	1 hr	0230	364
73	1 hr	0230	365
74	1 hr	0230	366
75	1 hr	0230	367
76	1 hr	0230	368
77	1 hr	0230	369
78	1 hr	0230	370
79	1 hr	0230	371
80	1 hr	0230	372
81	1 hr	0230	373
82	1 hr	0230	374
83	1 hr	0230	375
84	1 hr	0230	376
85	1 hr	0230	377
86	1 hr	0230	378
87	1 hr	0230	379
88	1 hr	0230	380
89	1 hr	0230	381
90	1 hr	0230	382
91	1 hr	0230	383
92	1 hr	0230	384
93	1 hr	0230	385
94	1 hr	0230	386
95	1 hr	0230	387
96	1 hr	0230	388
97	1 hr	0230	389
98	1 hr	0230	390
99	1 hr	0230	391
100	1 hr	0230	392
101	1 hr	0230	393
102	1 hr	0230	394
103	1 hr	0230	395
104	1 hr	0230	396
105	1 hr	0230	397
106	1 hr	0230	398
107	1 hr	0230	399
108	1 hr	0230	400
109	1 hr	0230	401
110	1 hr	0230	402
111	1 hr	0230	403
112	1 hr	0230	404
113	1 hr	0230	405
114	1 hr	0230	406
115	1 hr	0230	407
116	1 hr	0230	408
117	1 hr	0230	409
118	1 hr	0230	410
119	1 hr	0230	411
120	1 hr	0230	412
121	1 hr	0230	413
122	1 hr	0230	414
123	1 hr	0230	415
124	1 hr	0230	416
125	1 hr	0230	417
126	1 hr	0230	418
127	1 hr	0230	419
128	1 hr	0230	420
129	1 hr	0230	421
130	1 hr	0230	422
131	1 hr	0230	423
132	1 hr	0230	424
133	1 hr	0230	425
134	1 hr	0230	426
135	1 hr	0230	427
136	1 hr	0230	428
137	1 hr	0230	429
138	1 hr	0230	430
139	1 hr	0230	431
140	1 hr	0230	432
141	1 hr	0230	433
142	1 hr	0230	434
143	1 hr	0230	435
144	1 hr	0230	436
145	1 hr	0230	437
146	1 hr	0230	438
147	1 hr	0230	439
148	1 hr	0230	440
149	1 hr	0230	441
150	1 hr	0230	442
151	1 hr	0230	443
152	1 hr	0230	444
153	1 hr	0230	445
154	1 hr	0230	446
155	1 hr	0230	447
156	1 hr	0230	448
157	1 hr	0230	449
158	1 hr	0230	450
159	1 hr	0230	451
160	1 hr	0230	452
161	1 hr	0230	453
162	1 hr	0230	454
163	1 hr	0230	455
164	1 hr	0230	456
165	1 hr	0230	457
166	1 hr	0230	458
167	1 hr	0230	459
168	1 hr	0230	460
169	1 hr	0230	461
170	1 hr	0230	462
171	1 hr	0230	463
172	1 hr	0230	464
173	1 hr	0230	465
174	1 hr	0230	466
175	1 hr	0230	467
176	1 hr	0230	468
177	1 hr	0230	469
178	1 hr	0230	470
179	1 hr	0230	471
180	1 hr	0230	472
181	1 hr	0230	473
182	1 hr	0230	474
183	1 hr	0230	475
184	1 hr	0230	476
185	1 hr	0230	477
186	1 hr	0230	478
187	1 hr	0230	479
188	1 hr	0230	480
189	1 hr	0230	481
190	1 hr	0230	482
191	1 hr	0230	483
192	1 hr	0230	484
193	1 hr	0230	485
194	1 hr	0230	486
195	1 hr	0230	487
196	1 hr	0230	488
197	1 hr	0230	489
198	1 hr	0230	490
199	1 hr	0230	491
200	1 hr	0230	492
201	1 hr	0230	493
202	1 hr	0230	494
203	1 hr	0230	495
204	1 hr	0230	496
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208	1 hr	0230	500
209	1 hr	0230	501
210	1 hr	0230	502
211	1 hr	0230	503
212	1 hr	0230	504
213	1 hr	0230	505
214	1 hr	0230	506
215	1 hr	0230	507
216	1 hr	0230	508
217	1 hr	0230	509
218	1 hr	0230	510
219	1 hr	0230	511
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235	1 hr	0230	527
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237	1 hr	0230	529
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239	1 hr	0230	531
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252	1 hr	0230	544
253	1 hr	0230	545
254	1 hr	0230	546
255	1 hr	0230	547
256	1 hr	0230	548
257	1 hr	0230	549
258	1 hr	0230	550
259	1 hr	0230	551
260	1 hr	0230	552
261	1 hr	0230	553
262	1 hr	0230	554
263	1 hr	0230	555
264	1 hr	0230	556
265	1 hr	0230	557
266	1 hr	0230	558
267	1 hr	0230	559
268	1 hr	0230	560
269	1 hr	0230	561
270	1 hr	0230	562
271	1 hr	0230	563
272	1 hr	0230	564
273	1 hr	0230	565
274	1 hr	0230	566
275	1 hr	0230	567
276	1 hr	0230	568
277	1 hr	0230	569
278	1 hr	0230	570
279	1 hr	0230	571
280	1 hr	0230	572
281	1 hr	0230	573
282	1 hr	0230	574
283	1 hr	0230	575
284	1 hr	0230	576
285	1 hr	0230	577
286	1 hr	0230	578
287	1 hr	0230	579
288	1 hr	0230	580
289	1 hr	0230	581
290	1 hr	0230	582
291	1 hr	0230	583
292	1 hr	0230	584
293	1 hr	0230	585
294	1 hr	0230	586
295	1 hr	0230	587
296	1 hr	0230	588
297	1 hr	0230	589
298	1 hr	0230	590
299	1 hr	0230	591
300	1 hr	0230	592
301	1 hr	0230	

## Experiment 11

Deeray Sekhon - #261 - continued

Second-dose formulation of chloramphenicol  
Dosed on 2-28-69 12:00

Procedure	Time Post-Dose	Actual time	Actual dose, mg
1	15 min	15:40	1
2	time	16:00	1
3	1 hr	17:40	1.32
4	2 hr	19:15	1.27
5	4 hr	21:00	1.27
6	6 hr	22:45	1.27
7	8 hr	24:00	1.27
8	10 hr	00:15	1.27
9	12 hr	01:45	1.27
10	14 hr	03:15	1.27
11	16 hr	04:45	1.27
12	18 hr	06:15	1.27
13	20 hr	07:45	1.27
14	22 hr	09:15	1.27
15	24 hr	10:45	1.27
16	26 hr	12:15	1.27
17	28 hr	13:45	1.27
18	30 hr	15:15	1.27
19	32 hr	16:45	1.27
20	34 hr	18:15	1.27
21	36 hr	19:45	1.27
22	38 hr	21:15	1.27
23	40 hr	22:45	1.27
24	42 hr	00:15	1.27
25	44 hr	01:45	1.27
26	46 hr	03:15	1.27
27	48 hr	04:45	1.27
28	50 hr	06:15	1.27
29	52 hr	07:45	1.27
30	54 hr	09:15	1.27
31	56 hr	10:45	1.27
32	58 hr	12:15	1.27
33	60 hr	13:45	1.27
34	62 hr	15:15	1.27
35	64 hr	16:45	1.27
36	66 hr	18:15	1.27
37	68 hr	19:45	1.27
38	70 hr	21:15	1.27
39	72 hr	22:45	1.27
40	74 hr	00:15	1.27
41	76 hr	01:45	1.27
42	78 hr	03:15	1.27
43	80 hr	04:45	1.27
44	82 hr	06:15	1.27
45	84 hr	07:45	1.27
46	86 hr	09:15	1.27
47	88 hr	10:45	1.27
48	90 hr	12:15	1.27
49	92 hr	13:45	1.27
50	94 hr	15:15	1.27
51	96 hr	16:45	1.27
52	98 hr	18:15	1.27
53	100 hr	19:45	1.27
54	102 hr	21:15	1.27
55	104 hr	22:45	1.27
56	106 hr	00:15	1.27
57	108 hr	01:45	1.27
58	110 hr	03:15	1.27
59	112 hr	04:45	1.27
60	114 hr	06:15	1.27
61	116 hr	07:45	1.27
62	118 hr	09:15	1.27
63	120 hr	10:45	1.27
64	122 hr	12:15	1.27
65	124 hr	13:45	1.27
66	126 hr	15:15	1.27
67	128 hr	16:45	1.27
68	130 hr	18:15	1.27
69	132 hr	19:45	1.27
70	134 hr	21:15	1.27
71	136 hr	22:45	1.27
72	138 hr	00:15	1.27
73	140 hr	01:45	1.27
74	142 hr	03:15	1.27
75	144 hr	04:45	1.27
76	146 hr	06:15	1.27
77	148 hr	07:45	1.27
78	150 hr	09:15	1.27
79	152 hr	10:45	1.27
80	154 hr	12:15	1.27
81	156 hr	13:45	1.27
82	158 hr	15:15	1.27
83	160 hr	16:45	1.27
84	162 hr	18:15	1.27
85	164 hr	19:45	1.27
86	166 hr	21:15	1.27
87	168 hr	22:45	1.27
88	170 hr	00:15	1.27
89	172 hr	01:45	1.27
90	174 hr	03:15	1.27
91	176 hr	04:45	1.27
92	178 hr	06:15	1.27
93	180 hr	07:45	1.27
94	182 hr	09:15	1.27
95	184 hr	10:45	1.27
96	186 hr	12:15	1.27
97	188 hr	13:45	1.27
98	190 hr	15:15	1.27
99	192 hr	16:45	1.27
100	194 hr	18:15	1.27
101	196 hr	19:45	1.27
102	198 hr	21:15	1.27
103	200 hr	22:45	1.27
104	202 hr	00:15	1.27
105	204 hr	01:45	1.27
106	206 hr	03:15	1.27
107	208 hr	04:45	1.27
108	210 hr	06:15	1.27
109	212 hr	07:45	1.27
110	214 hr	09:15	1.27
111	216 hr	10:45	1.27
112	218 hr	12:15	1.27
113	220 hr	13:45	1.27
114	222 hr	15:15	1.27
115	224 hr	16:45	1.27
116	226 hr	18:15	1.27
117	228 hr	19:45	1.27
118	230 hr	21:15	1.27
119	232 hr	22:45	1.27
120	234 hr	00:15	1.27
121	236 hr	01:45	1.27
122	238 hr	03:15	1.27
123	240 hr	04:45	1.27
124	242 hr	06:15	1.27
125	244 hr	07:45	1.27
126	246 hr	09:15	1.27
127	248 hr	10:45	1.27
128	250 hr	12:15	1.27
129	252 hr	13:45	1.27
130	254 hr	15:15	1.27
131	256 hr	16:45	1.27
132	258 hr	18:15	1.27
133	260 hr	19:45	1.27
134	262 hr	21:15	1.27
135	264 hr	22:45	1.27
136	266 hr	00:15	1.27
137	268 hr	01:45	1.27
138	270 hr	03:15	1.27
139	272 hr	04:45	1.27
140	274 hr	06:15	1.27
141	276 hr	07:45	1.27
142	278 hr	09:15	1.27
143	280 hr	10:45	1.27
144	282 hr	12:15	1.27
145	284 hr	13:45	1.27
146	286 hr	15:15	1.27
147	288 hr	16:45	1.27
148	290 hr	18:15	1.27
149	292 hr	19:45	1.27
150	294 hr	21:15	1.27
151	296 hr	22:45	1.27
152	298 hr	00:15	1.27
153	300 hr	01:45	1.27
154	302 hr	03:15	1.27
155	304 hr	04:45	1.27
156	306 hr	06:15	1.27
157	308 hr	07:45	1.27
158	310 hr	09:15	1.27
159	312 hr	10:45	1.27
160	314 hr	12:15	1.27
161	316 hr	13:45	1.27
162	318 hr	15:15	1.27
163	320 hr	16:45	1.27
164	322 hr	18:15	1.27
165	324 hr	19:45	1.27
166	326 hr	21:15	1.27
167	328 hr	22:45	1.27
168	330 hr	00:15	1.27
169	332 hr	01:45	1.27
170	334 hr	03:15	1.27
171	336 hr	04:45	1.27
172	338 hr	06:15	1.27
173	340 hr	07:45	1.27
174	342 hr	09:15	1.27
175	344 hr	10:45	1.27
176	346 hr	12:15	1.27
177	348 hr	13:45	1.27
178	350 hr	15:15	1.27
179	352 hr	16:45	1.27
180	354 hr	18:15	1.27
181	356 hr	19:45	1.27
182	358 hr	21:15	1.27
183	360 hr	22:45	1.27
184	362 hr	00:15	1.27
185	364 hr	01:45	1.27
186	366 hr	03:15	1.27
187	368 hr	04:45	1.27
188	370 hr	06:15	1.27
189	372 hr	07:45	1.27
190	374 hr	09:15	1.27
191	376 hr	10:45	1.27
192	378 hr	12:15	1.27
193	380 hr	13:45	1.27
194	382 hr	15:15	1.27
195	384 hr	16:45	1.27
196	386 hr	18:15	1.27
197	388 hr	19:45	1.27
198	390 hr	21:15	1.27
199	392 hr	22:45	1.27
200	394 hr	00:15	1.27
201	396 hr	01:45	1.27
202	398 hr	03:15	1.27
203	400 hr	04:45	1.27
204	402 hr	06:15	1.27
205	404 hr	07:45	1.27
206	406 hr	09:15	1.27
207	408 hr	10:45	1.27
208	410 hr	12:15	1.27
209	412 hr	13:45	1.27
210	414 hr	15:15	1.27
211	416 hr	16:45	1.27
212	418 hr	18:15	1.27
213	420 hr	19:45	1.27
214	422 hr	21:15	1.27
215	424 hr	22:45	1.27
216	426 hr	00:15	1.27
217	428 hr	01:45	1.27
218	430 hr	03:15	1.27
219	432 hr	04:45	1.27
220	434 hr	06:15	1.27
221	436 hr	07:45	1.27
222	438 hr	09:15	1.27
223	440 hr	10:45	1.27
224	442 hr	12:15	1.27
225	444 hr	13:45	1.27
226	446 hr	15:15	1.27
227	448 hr	16:45	1.27
228	450 hr	18:15	1.27
229	452 hr	19:45	1.27
230	454 hr	21:15	1.27
231	456 hr	22:45	1.27
232	458 hr	00:15	1.27
233	460 hr	01:45	1.27
234	462 hr	03:15	1.27
235	464 hr	04:45	1.27
236	466 hr	06:15	1.27
237	468 hr	07:45	1.27
238	470 hr	09:15	1.27
239	472 hr	10:45	1.27
240	474 hr	12:15	1.27
241	476 hr	13:45	1.27
242	478 hr	15:15	1.27
243	480 hr	16:45	1.27
244	482 hr	18:15	1.27
245	484 hr	19:45	1.27
246	486 hr	21:15	1.27
247	488 hr	22:45	1.27
248	490 hr	00:15	1.27
249	492 hr	01:45	1.27
250	494 hr	03:15	1.27
251	496 hr	04:45	1.27
252	498 hr	06:15	1.27
253	500 hr	07:45	1.27
254	502 hr	09:15	1.27
255	504 hr	10:45	1.27
256	506 hr	12:15	1.27
257	508 hr	13:45	1.27
258	510 hr	15:15	1.27
259	512 hr	16:45	1.27
260	514 hr	18:15	1.27
261	516 hr	19:45	1.27
262	518 hr	21:15	1.27
263	520 hr	22:45	1.27
264	522 hr	00:15	1.27
265	524 hr	01:45	1.27
266	526 hr	03:15	1.27
267	528 hr	04:45	1.27
268	530 hr	06:15	1.27
269	532 hr	07:45	1.27
270	534 hr	09:15	1.27

Date: 8/28/62 Age: 11 Mf: Boy - A\* Wt: 75 Ht: 5

First-dose(s) Administration to 301 patients  
Dosed on 1-31-62 (8/28)

Time	Time	base	actual time	actual dose, mg/m
15	110		110.0	100
0	time		100.0	—
1	110		100.0	100
2	110		100.0	100
3	110		100.0	100
4	110		100.0	100
5	110		100.0	100
6	110		100.0	100
7	110		100.0	100
8	110		100.0	100
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18	110		100.0	100
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254	110		100.0	100
255	110		100.0	100
256	110		100.0	100
257	110		100.0	100
258	110		100.0	100
259	110		100.0	100
260				

Date 6/20/62 - Cont. sheet

**Second dosing formulation: Carbetaine**  
 Based on a 28.13 g/L dose

Sample No.	Time Post Dose	Actual Dose	Dose Calculated
1	15 min	0.745	0.9
2	0 time	0.610	0.7
3	1 min	0.600	0.7
4	2 min	0.590	0.7
5	3 min	0.580	0.7
6	4 min	0.570	0.7
7	5 min	0.560	0.7
8	6 min	0.550	0.7
9	7 min	0.540	0.7
10	8 min	0.530	0.7
11	9 min	0.520	0.7
12	10 min	0.510	0.7
13	11 min	0.500	0.7
14	12 min	0.490	0.7
15	13 min	0.480	0.7
16	14 min	0.470	0.7
17	15 min	0.460	0.7
18	16 min	0.450	0.7
19	17 min	0.440	0.7
20	18 min	0.430	0.7
21	19 min	0.420	0.7
22	20 min	0.410	0.7
23	21 min	0.400	0.7
24	22 min	0.390	0.7
25	23 min	0.380	0.7
26	24 min	0.370	0.7
27	25 min	0.360	0.7
28	26 min	0.350	0.7
29	27 min	0.340	0.7
30	28 min	0.330	0.7
31	29 min	0.320	0.7
32	30 min	0.310	0.7
33	31 min	0.300	0.7
34	32 min	0.290	0.7
35	33 min	0.280	0.7
36	34 min	0.270	0.7
37	35 min	0.260	0.7
38	36 min	0.250	0.7
39	37 min	0.240	0.7
40	38 min	0.230	0.7
41	39 min	0.220	0.7
42	40 min	0.210	0.7
43	41 min	0.200	0.7
44	42 min	0.190	0.7
45	43 min	0.180	0.7
46	44 min	0.170	0.7
47	45 min	0.160	0.7
48	46 min	0.150	0.7
49	47 min	0.140	0.7
50	48 min	0.130	0.7
51	49 min	0.120	0.7
52	50 min	0.110	0.7
53	51 min	0.100	0.7
54	52 min	0.090	0.7
55	53 min	0.080	0.7
56	54 min	0.070	0.7
57	55 min	0.060	0.7
58	56 min	0.050	0.7
59	57 min	0.040	0.7
60	58 min	0.030	0.7
61	59 min	0.020	0.7
62	60 min	0.010	0.7
63	61 min	0.000	0.7

## Experiment #10

Fred D. Amoani 4263 Age 55 Ht 5'8" Wt 145 lbs

First dosing formulation of Hoffmann-La Roche  
Dosed on 1-31-63 1200

Drug No.	Time Post Dose	Relative Value	Value in mg. 1000
1	15 min	1.00	0.0
2	time	0.90	0.0
3	1 hr	0.80	0.0
4	2 hr	0.70	0.0
5	4 hr	0.60	0.0
6	8 hr	0.40	0.0
7	12 hr	0.30	0.0
8	14 hr	0.20	0.0
9	15 hr	0.10	0.0
10	16 hr	0.05	0.0
11	17 hr	0.02	0.0
12	18 hr	0.01	0.0
13	19 hr	0.00	0.0
14	20 hr	0.00	0.0
15	21 hr	0.00	0.0
16	22 hr	0.00	0.0
17	23 hr	0.00	0.0
18	24 hr	0.00	0.0
19	25 hr	0.00	0.0
20	26 hr	0.00	0.0
21	27 hr	0.00	0.0
22	28 hr	0.00	0.0
23	29 hr	0.00	0.0
24	30 hr	0.00	0.0
25	31 hr	0.00	0.0
26	32 hr	0.00	0.0
27	33 hr	0.00	0.0
28	34 hr	0.00	0.0
29	35 hr	0.00	0.0
30	36 hr	0.00	0.0
31	37 hr	0.00	0.0
32	38 hr	0.00	0.0
33	39 hr	0.00	0.0
34	40 hr	0.00	0.0
35	41 hr	0.00	0.0
36	42 hr	0.00	0.0
37	43 hr	0.00	0.0
38	44 hr	0.00	0.0
39	45 hr	0.00	0.0
40	46 hr	0.00	0.0
41	47 hr	0.00	0.0
42	48 hr	0.00	0.0
43	49 hr	0.00	0.0
44	50 hr	0.00	0.0
45	51 hr	0.00	0.0
46	52 hr	0.00	0.0
47	53 hr	0.00	0.0
48	54 hr	0.00	0.0
49	55 hr	0.00	0.0
50	56 hr	0.00	0.0
51	57 hr	0.00	0.0
52	58 hr	0.00	0.0
53	59 hr	0.00	0.0
54	60 hr	0.00	0.0
55	61 hr	0.00	0.0
56	62 hr	0.00	0.0
57	63 hr	0.00	0.0
58	64 hr	0.00	0.0
59	65 hr	0.00	0.0
60	66 hr	0.00	0.0
61	67 hr	0.00	0.0
62	68 hr	0.00	0.0
63	69 hr	0.00	0.0
64	70 hr	0.00	0.0
65	71 hr	0.00	0.0
66	72 hr	0.00	0.0
67	73 hr	0.00	0.0
68	74 hr	0.00	0.0
69	75 hr	0.00	0.0
70	76 hr	0.00	0.0
71	77 hr	0.00	0.0
72	78 hr	0.00	0.0
73	79 hr	0.00	0.0
74	80 hr	0.00	0.0
75	81 hr	0.00	0.0
76	82 hr	0.00	0.0
77	83 hr	0.00	0.0
78	84 hr	0.00	0.0
79	85 hr	0.00	0.0
80	86 hr	0.00	0.0
81	87 hr	0.00	0.0
82	88 hr	0.00	0.0
83	89 hr	0.00	0.0
84	90 hr	0.00	0.0
85	91 hr	0.00	0.0
86	92 hr	0.00	0.0
87	93 hr	0.00	0.0
88	94 hr	0.00	0.0
89	95 hr	0.00	0.0
90	96 hr	0.00	0.0
91	97 hr	0.00	0.0
92	98 hr	0.00	0.0
93	99 hr	0.00	0.0
94	100 hr	0.00	0.0
95	101 hr	0.00	0.0
96	102 hr	0.00	0.0
97	103 hr	0.00	0.0
98	104 hr	0.00	0.0
99	105 hr	0.00	0.0
100	106 hr	0.00	0.0
101	107 hr	0.00	0.0
102	108 hr	0.00	0.0
103	109 hr	0.00	0.0
104	110 hr	0.00	0.0
105	111 hr	0.00	0.0
106	112 hr	0.00	0.0
107	113 hr	0.00	0.0
108	114 hr	0.00	0.0
109	115 hr	0.00	0.0
110	116 hr	0.00	0.0
111	117 hr	0.00	0.0
112	118 hr	0.00	0.0
113	119 hr	0.00	0.0
114	120 hr	0.00	0.0
115	121 hr	0.00	0.0
116	122 hr	0.00	0.0
117	123 hr	0.00	0.0
118	124 hr	0.00	0.0
119	125 hr	0.00	0.0
120	126 hr	0.00	0.0
121	127 hr	0.00	0.0
122	128 hr	0.00	0.0
123	129 hr	0.00	0.0
124	130 hr	0.00	0.0
125	131 hr	0.00	0.0
126	132 hr	0.00	0.0
127	133 hr	0.00	0.0
128	134 hr	0.00	0.0
129	135 hr	0.00	0.0
130	136 hr	0.00	0.0
131	137 hr	0.00	0.0
132	138 hr	0.00	0.0
133	139 hr	0.00	0.0
134	140 hr	0.00	0.0
135	141 hr	0.00	0.0
136	142 hr	0.00	0.0
137	143 hr	0.00	0.0
138	144 hr	0.00	0.0
139	145 hr	0.00	0.0
140	146 hr	0.00	0.0
141	147 hr	0.00	0.0
142	148 hr	0.00	0.0
143	149 hr	0.00	0.0
144	150 hr	0.00	0.0
145	151 hr	0.00	0.0
146	152 hr	0.00	0.0
147	153 hr	0.00	0.0
148	154 hr	0.00	0.0
149	155 hr	0.00	0.0
150	156 hr	0.00	0.0
151	157 hr	0.00	0.0
152	158 hr	0.00	0.0
153	159 hr	0.00	0.0
154	160 hr	0.00	0.0
155	161 hr	0.00	0.0
156	162 hr	0.00	0.0
157	163 hr	0.00	0.0
158	164 hr	0.00	0.0
159	165 hr	0.00	0.0
160	166 hr	0.00	0.0
161	167 hr	0.00	0.0
162	168 hr	0.00	0.0
163	169 hr	0.00	0.0
164	170 hr	0.00	0.0
165	171 hr	0.00	0.0
166	172 hr	0.00	0.0
167	173 hr	0.00	0.0
168	174 hr	0.00	0.0
169	175 hr	0.00	0.0
170	176 hr	0.00	0.0
171	177 hr	0.00	0.0
172	178 hr	0.00	0.0
173	179 hr	0.00	0.0
174	180 hr	0.00	0.0
175	181 hr	0.00	0.0
176	182 hr	0.00	0.0
177	183 hr	0.00	0.0
178	184 hr	0.00	0.0
179	185 hr	0.00	0.0
180	186 hr	0.00	0.0
181	187 hr	0.00	0.0
182	188 hr	0.00	0.0
183	189 hr	0.00	0.0
184	190 hr	0.00	0.0
185	191 hr	0.00	0.0
186	192 hr	0.00	0.0
187	193 hr	0.00	0.0
188	194 hr	0.00	0.0
189	195 hr	0.00	0.0
190	196 hr	0.00	0.0
191	197 hr	0.00	0.0
192	198 hr	0.00	0.0
193	199 hr	0.00	0.0
194	200 hr	0.00	0.0
195	201 hr	0.00	0.0
196	202 hr	0.00	0.0
197	203 hr	0.00	0.0
198	204 hr	0.00	0.0
199	205 hr	0.00	0.0
200	206 hr	0.00	0.0
201	207 hr	0.00	0.0
202	208 hr	0.00	0.0
203	209 hr	0.00	0.0
204	210 hr	0.00	0.0
205	211 hr	0.00	0.0
206	212 hr	0.00	0.0
207	213 hr	0.00	0.0
208	214 hr	0.00	0.0
209	215 hr	0.00	0.0
210	216 hr	0.00	0.0
211	217 hr	0.00	0.0
212	218 hr	0.00	0.0
213	219 hr	0.00	0.0
214	220 hr	0.00	0.0
215	221 hr	0.00	0.0
216	222 hr	0.00	0.0
217	223 hr	0.00	0.0
218	224 hr	0.00	0.0
219	225 hr	0.00	0.0
220	226 hr	0.00	0.0
221	227 hr	0.00	0.0
222	228 hr	0.00	0.0
223	229 hr	0.00	0.0
224	230 hr	0.00	0.0
225	231 hr	0.00	0.0
226	232 hr	0.00	0.0
227	233 hr	0.00	0.0
228	234 hr	0.00	0.0
229	235 hr	0.00	0.0
230	236 hr	0.00	0.0
231	237 hr	0.00	0.0
232	238 hr	0.00	0.0
233	239 hr	0.00	0.0
234	240 hr	0.00	0.0
235	241 hr	0.00	0.0
236	242 hr	0.00	0.0
237	243 hr	0.00	0.0
238	244 hr	0.00	0.0
239	245 hr	0.00	0.0
240	246 hr	0.00	0.0
241	247 hr	0.00	0.0
242	248 hr	0.00	0.0
243	249 hr	0.00	0.0
244	250 hr	0.00	0.0
245	251 hr	0.00	0.0
246	252 hr	0.00	0.0
247	253 hr	0.00	0.0
248	254 hr	0.00	0.0
249	255 hr	0.00	0.0
250	256 hr	0.00	0.0
251	257 hr	0.00	0.0
252	258 hr	0.00	0.0
253	259 hr	0.00	0.0
254	260 hr	0.00	0.0
255	261 hr	0.00	0.0
256	262 hr	0.00	0.0
257	263 hr	0.00	0.0
258	264 hr	0.00	0.0
259	265 hr	0.00	0.0
260	266 hr	0.00	0.0
261	267 hr	0.00	0.0
262	268 hr	0.00	0.0
263	269 hr	0.00	0.0
264	270 hr	0.00	0.0
265	271 hr	0.00	0.0
266	272 hr	0.00	0.0
267	273 hr	0.00	0.0
268	274 hr	0.00	0.0
269	275 hr	0.00	0.0
270	276 hr	0.00	0.0
271	277 hr	0.00	0.0
272	278 hr	0.00	0.0
273	279 hr	0.00	0.0
274	280 hr	0.00	0.0
275	281 hr	0.00	0.0
276	282 hr	0.00	0.0
277	283 hr	0.00	0.0
278	284 hr	0.00	0.0
279	285 hr	0.00	0.0
280	286 hr	0.00	0.0
281	287 hr	0.00	0.0
282	288 hr	0.00	0.0
283	289 hr	0.00	0.0
284	290 hr	0.00	0.0
285	291 hr	0.00	0.0
286	292 hr	0.00	0.0
287	293 hr	0.00	0.0
288	294 hr	0.00	0

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